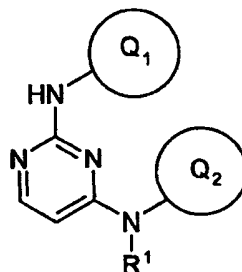




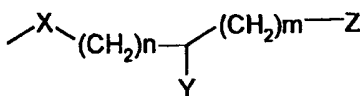
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 239/48, A61K 31/505		A1	(11) International Publication Number: WO 00/12485
			(43) International Publication Date: 9 March 2000 (09.03.00)
(21) International Application Number: PCT/GB99/02790 (22) International Filing Date: 24 August 1999 (24.08.99) (30) Priority Data: 9818989.7 29 August 1998 (29.08.98) GB 9828433.4 24 December 1998 (24.12.98) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BREAULT, Gloria, Anne [US/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). PEASE, Janet, Elizabeth [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (74) Agent: MACK, John, Richard; AstraZeneca PLC, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	

(54) Title: PYRIMIDINE COMPOUNDS



(I)



(Ia)

(57) Abstract

A pyrimidine derivative of formula (I) wherein, for example, R¹ is hydrogen, (1-6C)alkyl, (3-5C)alkenyl or (3-5C)alkynyl; Q₁ and Q₂ are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-tetrahydronaphthyl; and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link]; wherein, for example, X is CH₂, O, S or NH; Y is H or as defined for Z; Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂ or -NH-(3-8C)cycloalkyl; n is 1, 2 or 3; m is 1, 2 or 3; and Q₁ and Q₂ may optionally bear other substituents selected, for example, from halogeno, (1-6C)alkyl, cyano and (2-4C)alkenyl; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof; are useful as anti-cancer agents; and processes for their manufacture and pharmaceutical compositions containing them are described.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PYRIMIDINE COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically-acceptable salts or in-vivo-hydrolysable esters thereof, which possess anti-cancer (such as anti-cell-proliferative, anti-cell migration and/or apoptotic) activity and are therefore useful in
5 methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an anti-cancer (anti-cell-proliferation/migration and/or apoptotic) effect in a warm-blooded animal such as man.

10 A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these
15 factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

The recent convergence of oncogene and tumour suppressor gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling
20 pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

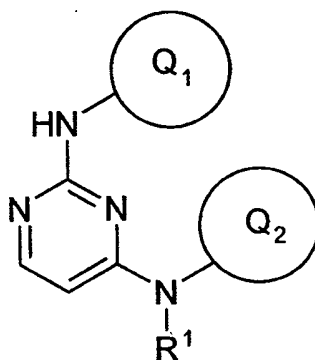
Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase
25 respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

Furthermore, it is believed that inhibition of focal adhesion kinase (FAK), which is involved in transduction signalling pathways, induces apoptosis (cell-death) and/or inhibits cell migration and an inhibitor of FAK may therefore have value as an anti-cancer agent.

30 The present invention is based on the discovery that certain 2,4-pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and

CDK6, and also inhibit FAK and thus possess anti-cancer (anti-cell-migration/proliferation and/or apoptotic) properties. Such properties are expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

According to the invention there is provided a pyrimidine derivative of the formula (I)



(I)

wherein

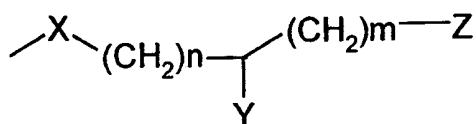
R¹ is selected from hydrogen, (1-6C)alkyl [optionally substituted by one or two substituents independently selected from halo, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, hydroxy, cyano, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl, -NHCO(1-4C)alkyl, trifluoromethyl, phenylthio, phenoxy, pyridyl, morpholino], benzyl, 2-phenylethyl, (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], N-phthalimido-(1-4C)alkyl, (3-5C)alkynyl [optionally substituted by one phenyl substituent] and (3-6C)cycloalkyl-(1-6C)alkyl;

wherein any phenyl or benzyl group in R¹ is optionally substituted by up to three substituents independently selected from halogeno, hydroxy, nitro, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, cyano, trifluoromethyl, (1-3C)alkyl [optionally substituted by 1 or 2 substituents independently selected from halogeno, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, hydroxy and trifluoromethyl], (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (3-5C)alkynyl, (1-3C)alkoxy, -SH, -S-(1-3C)alkyl, carboxy, (1-3C)alkoxycarbonyl;

Q_1 and Q_2 are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-tetrahydronaphthyl;

and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula (Ia) and Q_2 may optionally bear on any available carbon atom further substituents of

5 the formula (Ia)



(Ia)

[provided that when present in Q_1 the substituent of formula (Ia) is not adjacent to the -NH-link];

10 wherein

X is CH_2 , O, S, NH or NR_x [wherein R_x is (1-4C)alkyl, optionally substituted by one substituent selected from halo, amino, cyano, (1-4C)alkoxy or hydroxy];

Y is H or as defined for Z;

Z is OH, SH, NH_2 , (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂,

15 -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino;

n is 1, 2 or 3; m is 1, 2 or 3;

and Q_1 may optionally bear on any available carbon atom up to four substituents

20 independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],

(2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,

fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl,

di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl,

25 (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl,

carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl,

N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-

(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-

(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkylthio,

- (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido ($H_2N-CO-NH-$), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-
 5 [(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;
 and also independently, or where appropriate in addition to, the above substituents, Q_1 may optionally bear on any available carbon atom up to two further substituents independently selected from (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio,
 10 phenyl, naphthyl, benzoyl, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio and phenyl-(1-4C)alkoxy substituents may optionally bear up to five
 15 substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

- and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],
 20 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl,
 25 N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkoxy, cyano-(1-4C)alkoxy, carbamoyl-(1-4C)alkoxy, N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy,
N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy, 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy,
 30 2-di-[(1-4C)alkyl]aminoethoxy, (1-4C)alkoxycarbonyl-(1-4C)alkoxy, halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy,

2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy, (3-5C)alkenyloxy, (3-5C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H₂N-CO-NH-), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, 5 di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or where appropriate in addition to, the above optional substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents

10 independently selected from (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said

15 phenyl-(1-4C)alkyl, phenylthio, phenoxy and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

A suitable value for a ring substituent when it is a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms

20 independently selected from oxygen, sulphur and nitrogen) is, for example, pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or p-isoxazine.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight

25 chain version only. An analogous convention applies to other generic terms.

Suitable values for the generic radicals (such as in R¹ and in substituents on Q₁ and Q₂) referred to above include those set out below :-

when it is **halogeno** is, for example, fluoro, chloro, bromo and iodo; **(2-4C)alkenyl** is, for example, vinyl and allyl; when it is **(3-5C)alkenyl** is, for example, allyl or buten-3-yl; when it

30 is **(3-5C)alkynyl** is, for example, propyn-2-yl; when it is **(2-4C)alkynyl** is, for example, ethynyl and propyn-2-yl; when it is **(3-6C)cycloalkyl-(1-6C)alkyl** is, for example,

- cyclopropylmethyl; when it is (3-8C)cycloalkyl is, for example, cyclobutyl, cyclopentyl or cyclohexyl; when it is (1-4C)alkanoyl or (1-5C)alkanoyl is, for example, formyl and acetyl; when it is (1-4C)alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl; ; when it is (1-3C)alkyl is, for example, methyl,
- 5 ethyl, propyl, isopropyl; when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl; when it is (1-6C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl or 3-methylbutyl or hexyl; when it is **hydroxy**-(1-3C)alkyl is, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; when it is **hydroxy**-(2-4C)alkyl is, for example,
- 10 2-hydroxyethyl and 3-hydroxypropyl; when it is **fluoro**-(1-4C)alkyl is, for example, fluoromethyl, difluoromethyl, trifluoromethyl and 2-fluoroethyl; when it is **amino**-(1-3C)alkyl is, for example, aminomethyl, 1-aminoethyl and 2-aminoethyl; when it is (1-4C)alkylamino-(1-3C)-alkyl is, for example, methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
- 15 when it is **di**-[(1-4C)alkyl]amino-(1-3C)alkyl is, for example, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl; when it is **cyano**-(1-4C)alkyl is, for example cyanomethyl, 2-cyanoethyl and 3-cyanopropyl; when it is (2-4C)alkanoyloxy-(1-4C)-alkyl is, for example, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, 2-acetoxyethyl and 3-acetoxypropyl;
- 20 when it is (1-4C)alkoxy-(1-3C)alkyl is, for example, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl; when it is **carboxy**-(1-4C)alkyl is, for example carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl; when it is (1-4C)alkoxycarbonyl-(1-4C)alkyl is, for example, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl,
- 25 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl; when it is **carbamoyl**-(1-4C)alkyl is, for example carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl; when it is N-(1-4C)alkylcarbamoyl-(1-4C)alkyl is, for example, N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl,
- 30 N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 1-(N-ethylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N-ethylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;

- when it is N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl is, for example, N,N-dimethylcarbamoylmethyl, N-ethyl-N-methylcarbamoylmethyl, N,N-diethylcarbamoylmethyl, 1-(N,N-dimethylcarbamoyl)ethyl, 1-(N,N-diethylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl,
- 5 2-(N,N-diethylcarbamoyl)ethyl and 3-(N,N-dimethylcarbamoyl)propyl; when it is **pyrrolidin-1-yl-(1-3C)alkyl** is, for example, pyrrolidin-1-ylmethyl and 2-pyrrolidin-1-ylethyl; when it is **piperidin-1-yl-(1-3C)alkyl** is, for example, piperidin-1-ylmethyl and 2-piperidin-1-ylethyl; when it is **piperazin-1-yl-(1-3C)alkyl** is, for example, piperazin-1-ylmethyl and 2-piperazin-1-ylethyl; when it is **morpholino-(1-3C)alkyl** is, for example, morpholinomethyl and 2-
- 10 morpholinoethyl; when it is **thiomorpholino-(1-3C)alkyl** is, for example, thiomorpholinomethyl and 2-thiomorpholinoethyl; when it is **(1-4C)alkoxy** is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy; when it is **cyano-(1-4C)alkoxy** is, for example, cyanomethoxy, 1-cyanoethoxy, 2-cyanoethoxy and 3-cyanopropoxy; when it is **carbamoyl-(1-4C)alkoxy** is, for example, carbamoylmethoxy, 1-carbamoylethoxy,
- 15 2-carbamoylethoxy and 3-carbamoylpropoxy; when it is **N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy** is, for example, N-methylcarbamoylmethoxy, N-ethylcarbamoylmethoxy, 2-(N-methylcarbamoyl)ethoxy, 2-(N-ethylcarbamoyl)ethoxy and 3-(N-methylcarbamoyl)propoxy; when it is N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy is, for example,
- 20 N,N-dimethylcarbamoylmethoxy, N-ethyl-N-methylcarbamoylmethoxy, N,N-diethylcarbamoylmethoxy, 2-(N,N-dimethylcarbamoyl)ethoxy, 2-(N,N-diethylcarbamoyl)ethoxy and 3-(N,N-dimethylcarbamoyl)propoxy; when it is **2-(1-4C)alkylaminoethoxy** is, for example, 2-(methylamino)ethoxy, 2-(ethylamino)ethoxy and 2-(propylamino)ethoxy; when it
- 25 is **2-di-[(1-4C)alkyl]aminoethoxy** is, for example, 2-(dimethylamino)ethoxy, 2-(N-ethyl-N-methylamino)ethoxy, 2-(diethylamino)ethoxy and 2-(dipropylamino)ethoxy; when it is **(1-4C)alkoxycarbonyl-(1-4C)alkoxy** is, for example, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 1-methoxycarbonylethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy and
- 30 3-methoxycarbonylpropoxy; when it is **halogeno-(1-4C)alkoxy** is, for example, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy,

3-fluoropropoxy, 3-chloropropoxy and 2-chloro-2,1,1-trifluoroethoxy; when it is (2-4C)alkanoyloxy-(2-4C)alkoxy is, for example, 2-acetoxyethoxy, 2-propionyloxyethoxy, 2-butyryloxyethoxy and 3-acetoxypropoxy; when it is 2-(1-4C)alkoxyethoxy is, for example, 2-methoxyethoxy, 2-ethoxyethoxy; when it is carboxy-(1-4C)alkoxy is, for example, 5 carboxymethoxy, 1-carboxyethoxy, 2-carboxyethoxy and 3-carboxypropoxy; when it is (3-5C)alkenyloxy is, for example, allyloxy; when it is (3-5C)alkynyloxy is, for example, propynyloxy; when it is (1-4C)alkylthio is, for example, methylthio, ethylthio or propylthio; when it is (1-4C)alkylsulphinyl is, for example, methylsulphinyl, ethylsulphinyl or propylsulphinyl; when it is (1-4C)alkylsulphonyl is, for example, methylsulphonyl, 10 ethylsulphonyl or propylsulphonyl; when it is N-(1-4C)alkylcarbamoyl is, for example N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl; when it is N,N-di-[(1-4C)alkyl]-carbamoyl is, for example N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl; when it is (1-4C)alkylamino or (1-3C)alkylamino is, for example, methylamino, ethylamino or propylamino; when it is 15 di-[(1-4C)alkyl]amino or di-[(1-3C)alkyl]amino is, for example, dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino or dipropylamino; when it is (2-4C)alkanoylamino is, for example, acetamido, propionamido or butyramido; when it is phenyl-(1-4C)alkyl is, for example benzyl or 2-phenylethyl; when it is phenyl-(1-4C)alkoxy is, for example benzyloxy; when it is -NHCO(1-4C)alkyl is, for example acetamido; when it 20 is N-phthalimido-(1-4C)alkyl is, for example 2-(N-phthalimido)ethyl or 3-(N-phthalimido)propyl.

A suitable pharmaceutically-acceptable salt of a pyrimidine derivative of the invention is, for example, an acid-addition salt of a pyrimidine derivative of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or 25 organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a pyrimidine derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a 30 physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine, tris-(2-hydroxyethyl)amine, N-methylpiperidine,

N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, N-methyl deglucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

5 However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

In another embodiment there is provided a compound of formula (I) wherein R¹ is selected from hydrogen, (1-6C)alkyl [optionally substituted by one or two substituents independently selected from halo, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, hydroxy, 10 cyano, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl, -NHCO(1-4C)alkyl, trifluoromethyl, phenylthio, phenoxy], benzyl, (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], N-phthalimido-(1-4C)alkyl, (3-5C)alkynyl and (3-6C)cycloalkyl-(1-6C)alkyl; wherein any phenyl or benzyl group in R¹ is optionally substituted by up to three substituents 15 independently selected from halogeno, hydroxy, nitro, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, cyano, trifluoromethyl, (1-3C)alkyl [optionally substituted by 1 or 2 substituents independently selected from halogeno, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, hydroxy and trifluoromethyl], (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (3-5C)alkynyl, 20 (1-3C)alkoxy, -SH, -S-(1-3C)alkyl, carboxy, (1-3C)alkoxycarbonyl;

Q₁ and Q₂ are both phenyl;

and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of the formula (Ia) and Q₂ may bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the - 25 NH- link];

wherein; X is CH₂, O, NH or S; Y is H or as defined for Z; Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino; n is 1, 2 or 3; m is 1, 2 or 3;

and Q₁ may optionally bear on any available carbon atom up to four substituents 30 independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],

(2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-3C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl,

5 carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, ureido (H₂N-CO-NH-), (1-4C)alkylNH-CO-NH-

10 , di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;

and also independently, or in addition to, the above substituents, Q₁ may optionally bear on any available carbon atom up to two further substituents independently selected from

15 phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenyl, naphthyl, benzoyl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl and phenyl-(1-4C)alkoxy substituents may optionally bear one or two

20 substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-3C)alkyl,

25 fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-

30 (1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-

- (1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkoxy, cyano-(1-4C)alkoxy, carbamoyl-(1-4C)alkoxy, N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy, 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy, 2-di-[(1-4C)alkyl]aminoethoxy, (1-4C)alkoxycarbonyl-(1-4C)alkoxy,
- 5 halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy, 2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy, (3-5C)alkenyloxy, (3-5C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, ureido (H₂N-CO-NH-), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-
- 10 [(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents independently selected from phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenyl, naphthyl, benzoyl and a 5- or 6-membered
- 15 aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl and phenyl-(1-4C)alkoxy substituents may optionally bear one or two substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a
- 20 pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

- In a further embodiment there is provided a compound of formula (I) wherein R¹ is selected from hydrogen, (1-6C)alkyl [optionally substituted by one or two substituents independently selected from halo, amino, (1-4C)alkylamino, di-(1-4C)alkylamino, hydroxy, cyano, (1-4C)alkoxy, (1-4C)alkoxycarbonyl and carbamoyl], benzyl, (2-4C)alkenyl,
- 25 (2-5C)alkynyl and (3-6C)cycloalkyl-(1-6C)alkyl;
- Q₁ and Q₂ are both phenyl;
- and one or both of Q₁ and Q₂ bears on any available carbon atom that is not adjacent to the -NH- or -NR¹- link one substituent of the formula (Ia) and Q₂ may bear on any available carbon atom that is not adjacent to the -NR¹- link further substituents of the formula (Ia)

wherein; X is CH₂, O, NH or S; Y is H or as defined for Z; Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino; n is 1, 2 or 3; m is 1, 2 or 3;

and Q₁ may optionally bear on any available carbon atom up to four substituents

- 5 independently selected from halogeno, thioxo, nitro, carboxy, cyano, (2-4C)alkenyl, (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, hydroxy-(1-3C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl,
- 10 carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, ureido, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino,
- 15 (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenyl, naphthyl, benzoyl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said
- 20 phenyl-(1-4C)alkyl and phenyl-(1-4C)alkoxy substituents may optionally bear one or two substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, oxo, thioxo, nitro, carboxy, cyano, (2-4C)alkenyl, (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, hydroxy-
- 25 (1-3C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl,
- 30 pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, (1-4C)alkoxy, cyano-(1-4C)alkoxy,

carbamoyl-(1-4C)alkoxy, N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy,
N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy, 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy,
 2-di-[(1-4C)alkyl]aminoethoxy, (1-4C)alkoxycarbonyl-(1-4C)alkoxy,
 halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy,
 5 2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy,
 (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, ureido, carbamoyl,
 N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-
 [(1-4C)alkyl]amino, (2-4C)alkanoylamino, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenyl,
 naphthyl, benzoyl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon
 10 atom and containing one to three heteroatoms independently selected from oxygen, sulphur
 and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic
 heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl and phenyl-
 (1-4C)alkoxy substituents may optionally bear one or two substituents independently selected
 from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a pharmaceutically-acceptable salt or in-
 15 vivo-hydrolysable ester thereof.

In the above mentioned embodiments, yet further embodiments are those as described
 above but in which Q₁ does not bear any of the additional substituents that contain a phenyl
 group, for example a phenyl-(1-4C)alkyl substituent.

The compounds of the formula (I) may be administered in the form of a pro-drug
 20 which is broken down in the human or animal body to give a compound of the formula (I). A
 prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the
 parent compound and can be formed when the parent compound contains a suitable group or
 substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-
 vivo hydrolysable esters of a compound of the formula (I) or a pharmaceutically-acceptable
 25 salt thereof.

Various forms of prodrugs are known in the art, for examples see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in
 Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and
 30 H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191
 (1991);

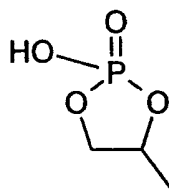
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-
5 acceptable salt thereof containing carboxy or hydroxy group is, for example, a
pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to
produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy
include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl
esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy-
10 (1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl
esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl
esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in
the compounds of this invention.

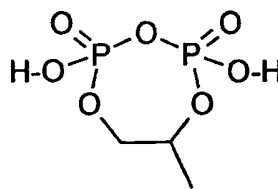
An in-vivo hydrolysable ester of a compound of the formula (I) or a pharmaceutically-
15 acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as
phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and
related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give
the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and
2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups
20 for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and
phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters),
di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give
carbamates), di-(1-4C)alkylaminoacetyl and carboxyacetyl. Examples of substituents on
benzoyl include chloromethyl, aminomethyl, (1-4C)alkylaminomethyl and
25 di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom
via a methylene linking group to the 3- or 4-position of the benzoyl ring.

Certain suitable in-vivo hydrolysable esters of a compound of the formula (I) are
described within the definitions listed in this specification. Further suitable in-vivo
hydrolysable esters of a compound of the formula (I) are described as follows. For example, a
30 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a pyrophosphate of
formula (PD2) :

- 15 -



(PD1)

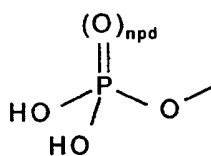


(PD2)

Esters of compounds of formula (I) wherein the HO- function/s in (PD1) and (PD2) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of formula (I) in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD3) :

10



(PD3)

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD3) in which either or both of the -OH groups in (PD3) is independently protected by (1-4C)alkyl, phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2) and (PD3) may be prepared by reaction of a compound of formula (I) containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

When a compound of formula (I) contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-trimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be

formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2) and/or (PD3) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo hydrolysable ester prodrug of a compound of formula (I) contains two (PD3) groups, there are
5 four HO-P- functionalites present in the overall molecule, each of which may form an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such
10 optical, diastereo-isomers and geometric isomers, and mixtures thereof, that possess CDK and/or FAK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK and/or FAK inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in
15 solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK and/or FAK inhibitory activity.

Particular preferred compounds of the invention comprise a pyrimidine derivative of the formula (I), or pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof,
20 wherein R¹, Q₁, Q₂, X, Y, Z, m and n have any of the meanings defined hereinbefore, or any of the following values. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

(a0) When Q₁ or Q₂ is indanyl or 1,2,3,4-tetrahydronaphthyl, it is linked via the unsaturated ring; preferably Q₁ and/or Q₂ are phenyl;

25 (a1) R¹ is preferably hydrogen in one embodiment;

(a2) In another embodiment R¹ is preferably hydrogen, benzyl, (3-5C)alkynyl (especially propyn-2-yl), (3-6C)cycloalkyl-(1-6C)alkyl (especially cyclopropylmethyl), (1-4C)alkyl [optionally substituted by one or two substituents selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups;

30 (b) R¹ is preferably benzyl, (3-5C)alkynyl (especially propyn-2-yl), (3-6C)cycloalkyl-(1-6C)alkyl (especially cyclopropylmethyl), (1-4C)alkyl [optionally substituted

- by one substituent selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one halo group;
- (c) R^1 is more preferably (3-5C)alkynyl (especially propyn-2-yl) or (1-4C)alkyl [optionally substituted by trifluoromethyl or cyano] or (3-5C)alkenyl substituted by one
- 5 bromo group;
- (d) R^1 is most preferably propyn-2-yl, (1-4C)alkyl substituted by one trifluoromethyl or one cyano group (especially cyanomethyl or 2-cyanoethyl) or (3-5C)alkenyl substituted by one bromo group (especially $-\text{CH}_2\text{CH}=\text{CHBr}$);
- (e) R^1 is most especially preferred as $-\text{CH}_2\text{CH}=\text{CHBr}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$ or -
- 10 $\text{CH}_2\text{CH}=\text{CH}$ -phenyl;
- (e1) In another embodiment R^1 is preferred as propyn-2-yl, cyanomethyl, 2-cyanoethyl, $-\text{CH}_2\text{CH}=\text{CHBr}$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$ (especially $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$);
- (f) In one embodiment Z is preferably $-\text{NH}(1-4\text{C})\text{alkyl}$, $-\text{N}[(1-4\text{C})\text{alkyl}]_2$,
- 15 $-\text{NH}(3-8\text{C})\text{cycloalkyl}$, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino; or alternatively Z is NH_2 ;
- (f1) In one embodiment Y is preferably H, OH, SH, NH_2 , (1-4C)alkoxy, (1-4C)alkylthio, $-\text{NH}(1-4\text{C})\text{alkyl}$, $-\text{N}[(1-4\text{C})\text{alkyl}]_2$ or $-\text{NH}(3-8\text{C})\text{cycloalkyl}$; especially H or
- 20 OH;
- (f2) In one embodiment X is preferably O or NH or NR_x ; least preferred is X as S;
- (f3) Preferably $n+m$ is less than 5;
- (f3) Preferably in the substituent of formula (Ia) X is O, Y is H or OH and Z is $-\text{NH}(1-4\text{C})\text{alkyl}$, $-\text{N}[(1-4\text{C})\text{alkyl}]_2$ or $-\text{NH}(3-8\text{C})\text{cycloalkyl}$; preferably n is 1 and m is 1;
- 25 (f4) In another embodiment in the substituent of formula (Ia) X is O, Y is OH and Z is $-\text{N}[(1-4\text{C})\text{alkyl}]_2$; preferably n is 1 and m is 1;
- (g) Most preferably the substituent of formula (Ia) is 3-dimethylamino-2-hydroxypropoxy;
- (h) Preferably there is one substituent of formula (Ia), and this substituent is in ring
- 30 Q_1 ;
- (i) When the substituent of formula (Ia) is in Q_1 it must be in either the para- or

meta- position relative to the -NH-, preferably in the para-position;

- (j) Preferably Q_1 bears no further substituents (other than (Ia)); preferable further substituents for Q_2 include halo, hydroxy-(1-3C)alkyl, fluoro-(1-4C)alkyl (especially trifluoromethyl), morpholino and (1-4C)alkyl (especially methyl);
- 5 (k) More preferable further substituents for Q_2 include halo, morpholino and (1-4C)alkyl (especially methyl);
- (l) Preferably the ring Q_1 or Q_2 not bearing the substituent of formula (Ia) is substituted by one or two further substituents, preferably halo, morpholino and/or (1-4C)alkyl (especially methyl);
- 10 (m) Most preferably the ring Q_1 bears the substituent of formula (Ia) and Q_2 is substituted by one or two further substituents, selected preferably from halo, hydroxy-(1-3C)alkyl, fluoro-(1-4C)alkyl (especially trifluoromethyl), morpholino and (1-4C)alkyl (especially methyl).

- A preferred compound of the invention is a pyrimidine derivative of the formula
- 15 (I), or pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof as claimed in any of claims 1 to 5 and wherein (i) Q_2 does not bear any optional further substituents of formula (Ia) and/or (ii) there is one substituent of formula (Ia), borne by Q_1 and/or (iii) in claims 1 or 2 Q_1 does not bear any of the additional two further substituents that are listed.

- A further preferred compound of the invention is a pyrimidine derivative of the
- 20 formula (I), or pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein:

- Q_1 and Q_2 are both phenyl;
- R^1 is hydrogen or (1-4C)alkyl substituted by one cyano group (especially cyanomethyl); or alternatively R^1 is $-\text{CH}_2\text{CH}=\text{CHBr}$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$ (especially $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$) or
- 25 $-\text{CH}_2\text{CH}=\text{CH-phenyl}$;
- Q_1 bears one substituent of formula (Ia) (especially 3-dimethylamino-2-hydroxypropoxy), preferably in the para-position;
- Q_2 bears one or two substituents independently selected from halo, morpholino and (1-4C)alkyl (especially methyl).
- 30 A specific preferred compound of the invention is the following pyrimidine derivative of the formula (I):-

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-bromo-4-methylanilino)pyrimidine
2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloroanilino)pyrimidine; or pharmaceutically-acceptable salt or *in-vivo* hydrolysable ester thereof.

Other specific preferred compounds of the invention are the pyrimidine derivatives of the formula (I), described in Examples 9, 20, 27, 29, 32, 56, 60, 37, 41, 42, 78, 80 and 82, or pharmaceutically-acceptable salts or *in-vivo* hydrolysable esters thereof.

Process Section

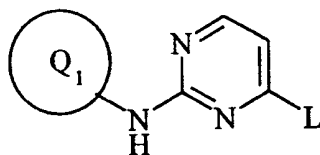
A pyrimidine derivative of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a pyrimidine derivative of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated R^1 , Q_1 , Q_2 , X, Y, Z, m and n have any of the meanings defined hereinbefore for a pyrimidine derivative of the formula (I) and unless another substituent is drawn on ring Q_1 or Q_2 the ring may bear any of the substituents described hereinbefore (optionally protected as necessary). Where a substituent is drawn on ring Q_1 , this includes (unless stated otherwise) the possibilities of the substituent/s being on ring Q_2 in addition to, or instead of the substituent being on ring Q_1 . Where X is defined in this process section as NH it is to be understood that this also includes the possibility of X as NR_x.

Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March - also useful for general guidance on reaction conditions and reagents). The preparation of such starting materials is described within the accompanying non-limiting processes and Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus, as a further feature of the invention there are provided the following processes which comprises of :-

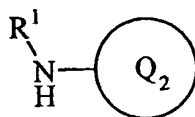
a) reacting a pyrimidine of formula (II):

- 20 -



(II)

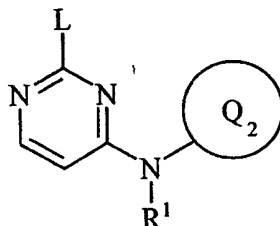
wherein L is a displaceable group as defined below, with a compound of formula (III):



(III)

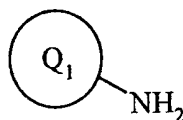
5

b) reaction of a pyrimidine of formula (IV):



(IV)

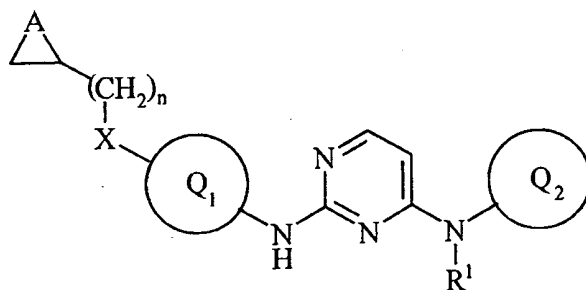
10 wherein L is a displaceable group as defined below, with a compound of formula (V):



(V)

c) for compounds of formula (I) wherein n is 1, 2 or 3; m = 1 and Y is OH, NH₂ or SH :

15 reaction of a 3-membered heteroalkyl ring of formula (VI):



(VI)

- 21 -

wherein A is O, S or NH;

with a nucleophile of formula (VII):

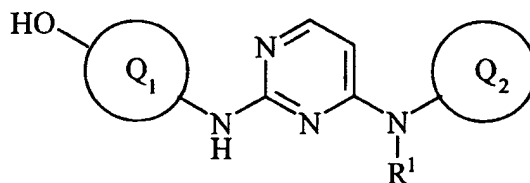
$$\text{Z-D}$$

(VII)

5 wherein D is H or a suitable counter-ion;

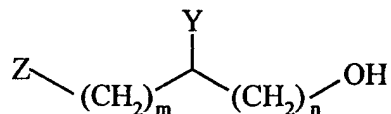
d) for compounds of formula (I) where X is oxygen :

by reaction of an alcohol of formula (VIII):



(VIII)

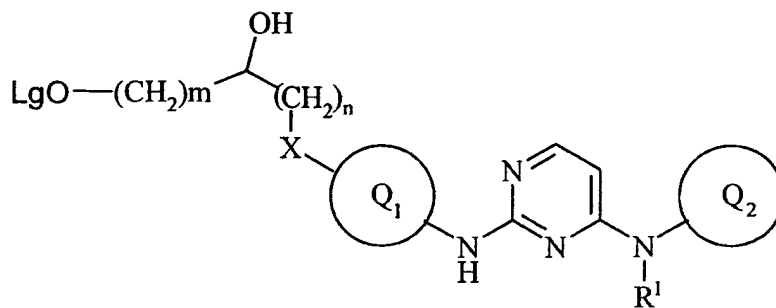
10 with an alcohol of formula (IX):



(IX)

e) for compounds of formula (I) wherein X is CH₂, O, NH or S; Y is OH and m is 2 or 3 :

15 reaction of a compound of formula (X) :



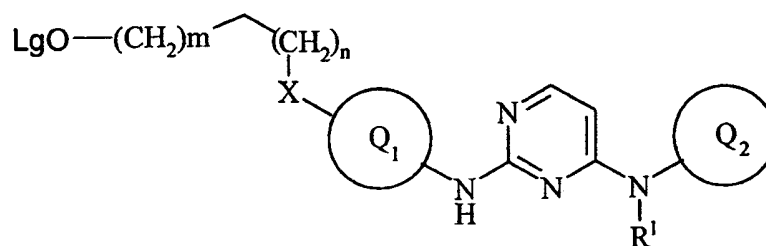
(X)

20 wherein -OLg is a leaving group such as mesylate or tosylate; with a nucleophile of formula Z-D (VII) wherein D is H or a suitable counter-ion;

- 22 -

f) for compounds of formula (I) wherein X is CH₂, O, NH or S; Y is H; n is 1, 2 or 3 and m is 1, 2 or 3 :

reaction of a compound of formula (XI) :

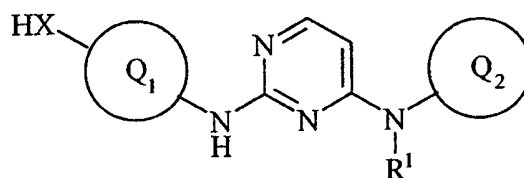


(XI)

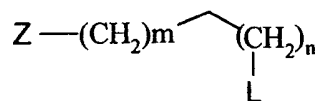
wherein -OLg is a leaving group such as mesylate or tosylate; with a nucleophile of formula Z-D (VII) wherein D is H or a suitable counter-ion;

g) for compounds of formula (I) wherein X is O, NH or S; Y is H; n is 1, 2 or 3 and m is 1, 2 or 3 :

reaction of a compound of formula (XII) with a compound of formula (XIII) :



(XII)



(XIII)

h) for compounds of formula (I) in which Z is SH, by conversion of a thioacetate group in a corresponding compound;
and thereafter if necessary:

- i) converting a compound of the formula (I) into another compound of the formula (I);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno or
5 sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

D is hydrogen or a counter-ion. When D is a counter-ion, suitable values for D include sodium and potassium.

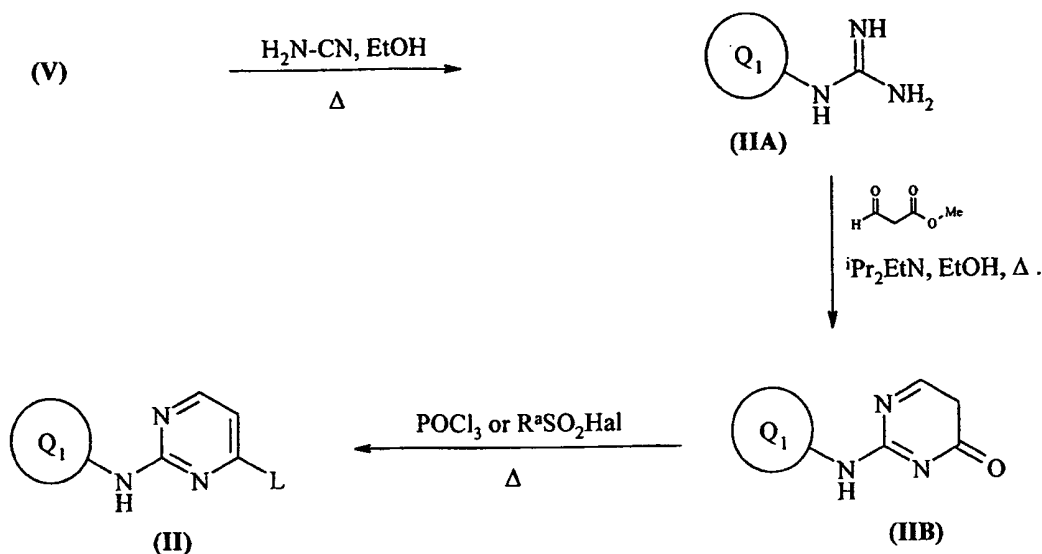
Specific reaction conditions for the above reactions are as follows:-

10 Process a)

Pyrimidines of formula (II) and anilines of formula (III) may be reacted together

- i) optionally in the presence of a suitable acid, for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid. The reaction is preferably carried out in a suitable inert solvent or diluent, for example
15 dichloromethane (DCM), acetonitrile, butanol, tetramethylene sulphone, tetrahydrofuran, 1,2-dimethoxyethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methylpyrrolidin-2-one, and at a temperature in the range, for example, 0° to 150°C, conveniently at or near reflux temperature; or
- ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am.*
20 *Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to
25 80°C.

Pyrimidines of the formula (II) may be prepared according to the following scheme:



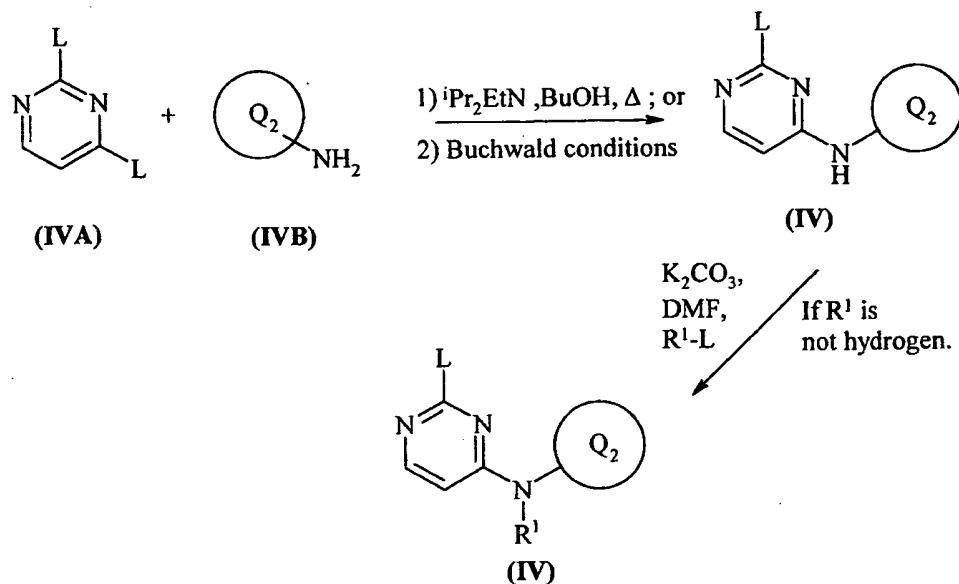
wherein R^a is an optionally substituted alkyl or aryl group. Preferably R^a is methyl, ethyl or p-tolyl.

Anilines of formula (III) are commercially available or are prepared by processes
5 known in the art.

Process b)

- Pyrimidines of formula (IV) and anilines of formula (V) may be reacted together, i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or N-methyl pyrrolidine,
10 optionally in the presence of a suitable acid such as those defined above (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or
ii) under standard Buchwald conditions as described above.

Pyrimidines of formula (IV) are prepared according to the following scheme :



wherein L is a displaceable group as defined above and R¹ is not hydrogen.

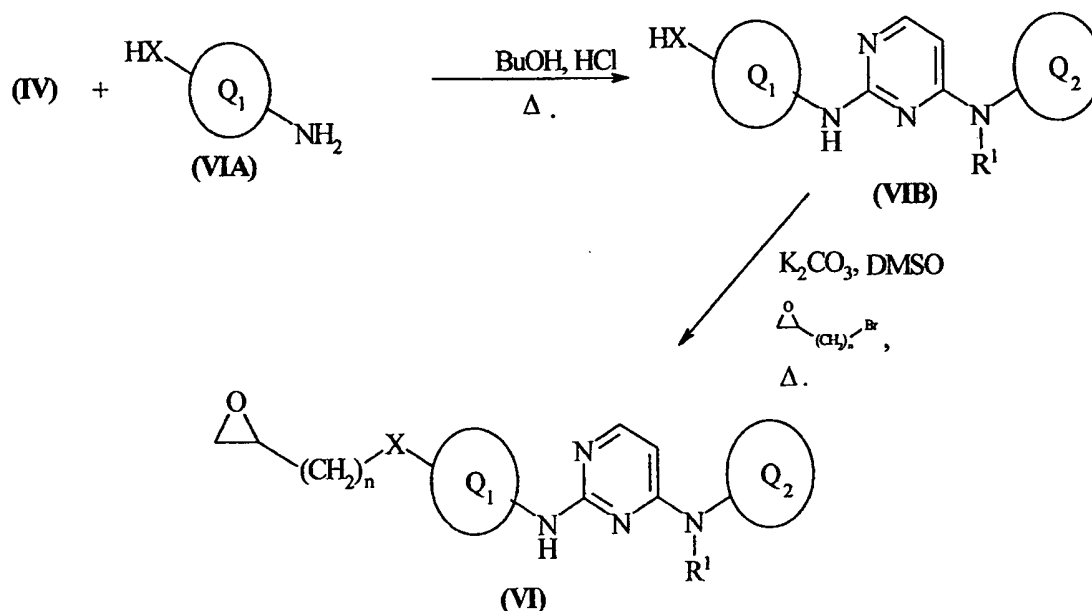
The anilines of formula (V) are commercially available or are prepared by processes known in the art.

5 Process c)

Three membered heteroalkyl rings of formula (VI) and nucleophiles of formula (VII) are reacted together at a temperature in the range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example N,N-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran.

10 Compounds formula (VI) may be prepared according to the following schemes:

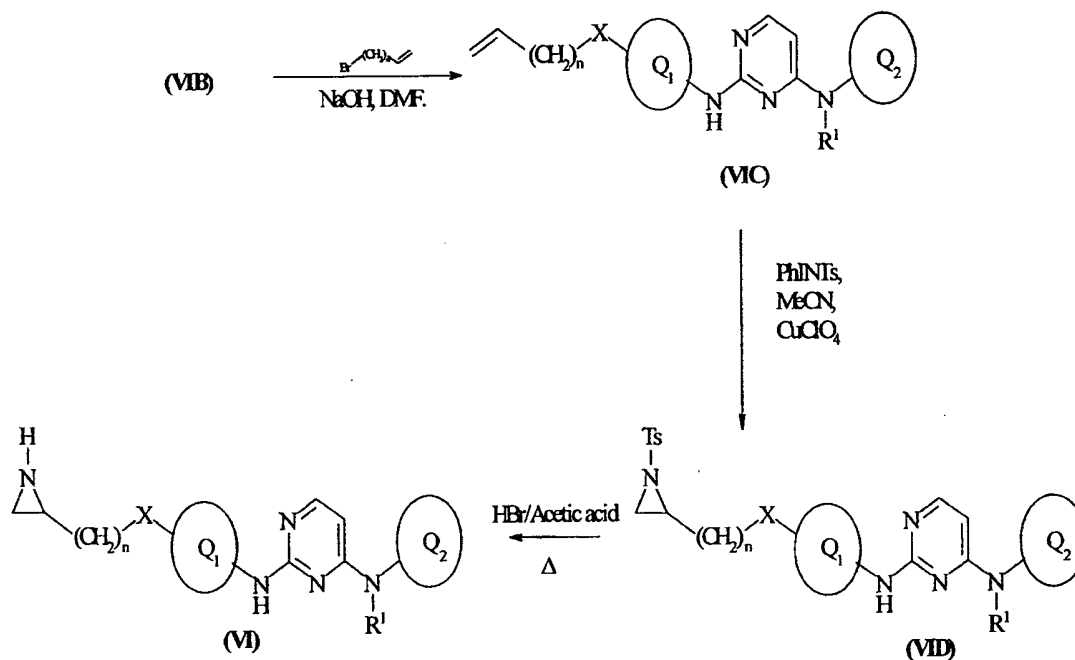
Scheme I) For compounds of formula (VI) where A is O, and X is not carbon :



The conversion of (VIB) to (VI) may also be achieved by reaction with $\text{Br} \text{---} (\text{CH}_2)_n \text{---} \text{CHO}$, or an equivalent ester, in DMF and the presence of a base, followed by reaction with a sulfur ylide such as $(\text{Me}_2\text{SOCH}_2)$ in an inert solvent such as THF (see Scheme V).

5

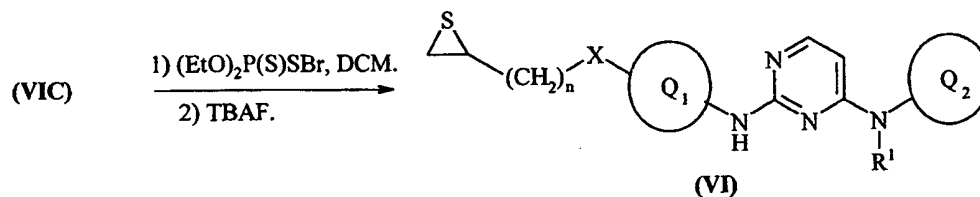
Scheme II) For compounds of formula (VI) where A is NH, and X is not carbon :



(for PhINTs see, for example, Tet.Let., 1997, 38 (39), 6897-6900; compounds of formula (VIC) may also be oxidised to the epoxide using conditions similar to that in Scheme IV)

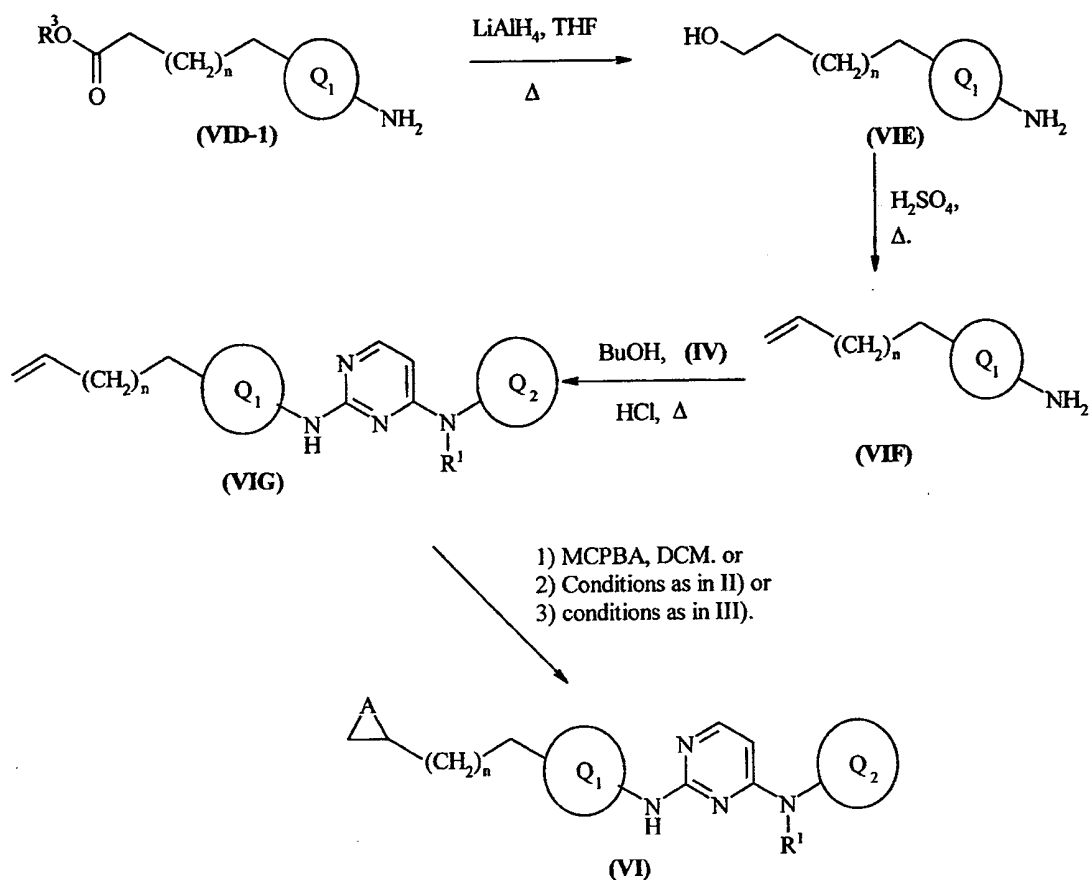
10 below);

Scheme III For compounds of formula (VI) where A is S, and X is not carbon :



(for example see *Synlett*, 1994, 267-268);

5 Scheme IV For compounds of formula (VI) where X is carbon :



wherein R³ together with the -COO- group to which it is attached forms an ester moiety, for example a methyl ester or an ethyl ester.

10 Scheme V For compounds of formula (VI) wherein X is CH₂, O, NH or S; Y is OH; n is 1, 2 or 3 and m is 1 :

An equivalent ester of (XA) may also be used. See also Russ.Chem. Rev. 47, 975-978.

Process d)

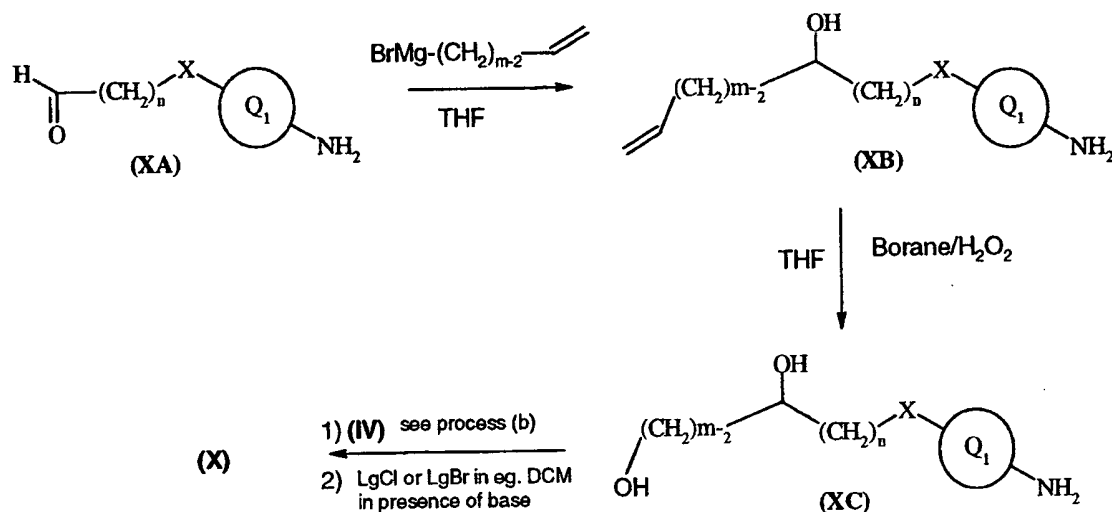
Alcohols of formula (VIII) are made according to the process in I) above for the synthesis of intermediate (VIB) (where X is oxygen),

In a process analogous to process d), compounds in which X is S may be prepared by reaction of a compound of formula (VIII) in which the hydroxy group is -SH, with a compound of formula (IX) in which the hydroxy group is a leaving group such as mesylate or tosylate.

Compounds of formula (X) wherein X is CH₂, O, NH or S; Y is OH and m is 2 or 3 and nucleophiles of formula (VII) are reacted together at a temperature in the range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example N,N-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran, and optionally in the presence of a suitable base, such as potassium carbonate.

Compounds of formula (X) are prepared according to the following scheme (m is 2 or 3):

- 29 -



The steps 1) and 2) in the final step may be reversed. A suitable base for step 2) is triethylamine.

Compounds of formula (XA) and (VII) are commercially available or are prepared by processes known in the art. For example, compounds of formula (XA) in which X is NH, O or S may be prepared by reaction of a compound of formula (VIA) with a suitable haloaldehyde or equivalent ester under standard conditions for such reactions.

Process f)

Compounds of formula (XI) and nucleophiles of formula (VII) are reacted together as described for process e) above.

Compounds of formula (XI) are prepared in an analogous manner to step 2) in the final step of the process for preparing compounds of formula (X) above. The necessary primary alcohol starting materials are commercially available or are prepared by processes known in the art.

Process g)

Compounds of formula (XII) and (XIII) are reacted in an inert solvent such as DMF in the presence of a base such as potassium carbonate.

Compounds of formula (XII) are of the same generic formula as compounds of formula (VIB) described herein and are prepared as described for those compounds (see Scheme I). Compounds of formula (XIII) are commercially available or are prepared by processes known in the art.

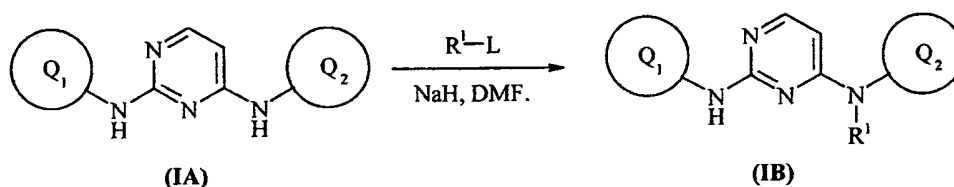
Process h)

For the compounds of formula **(I)** in which Z is SH, the conversion of a thioacetate group in a corresponding compound is carried out as described herein for the conversion of compounds of formula **(IJ)** into **(IK)**.

- 5 Suitable starting materials containing a thioacetate group are prepared from corresponding compounds containing a leaving group such as mesylate or tosylate (prepared using standard conditions from the corresponding hydroxy compound) using thiol acetic acid as described herein for the conversion of compounds of formula **(IG)** into **(IJ)**.

- 10 Examples of conversions of a compound of formula **(I)** into another compound of formula **(I)** are:

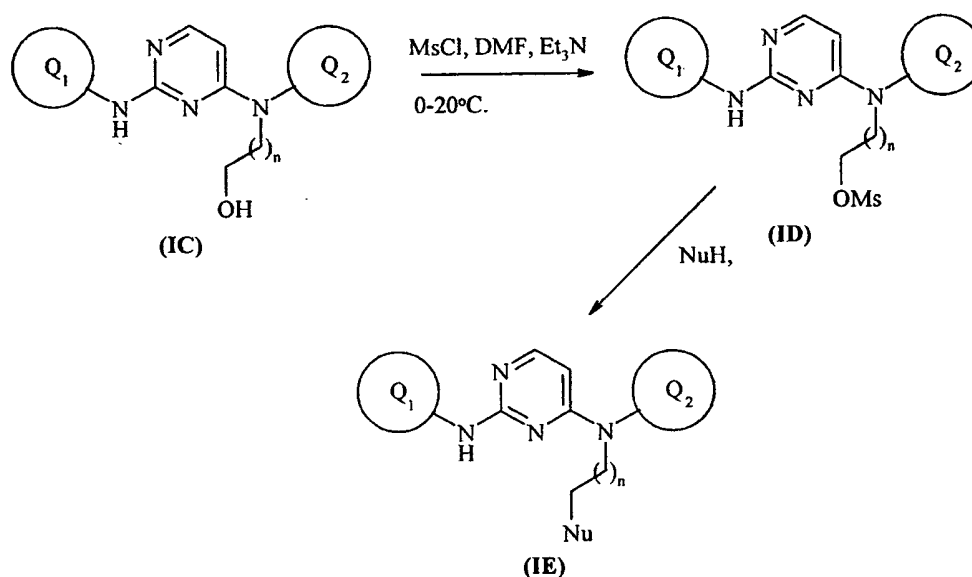
Conversion i) : conversion of R¹ as hydrogen into other R¹ for example:



wherein L is a displaceable group as defined above and R¹ in the above diagram is not equal

- 15 to hydrogen;

Conversion ii) : conversion of R¹ as a substituted side chain into another substituted side chain, for example:



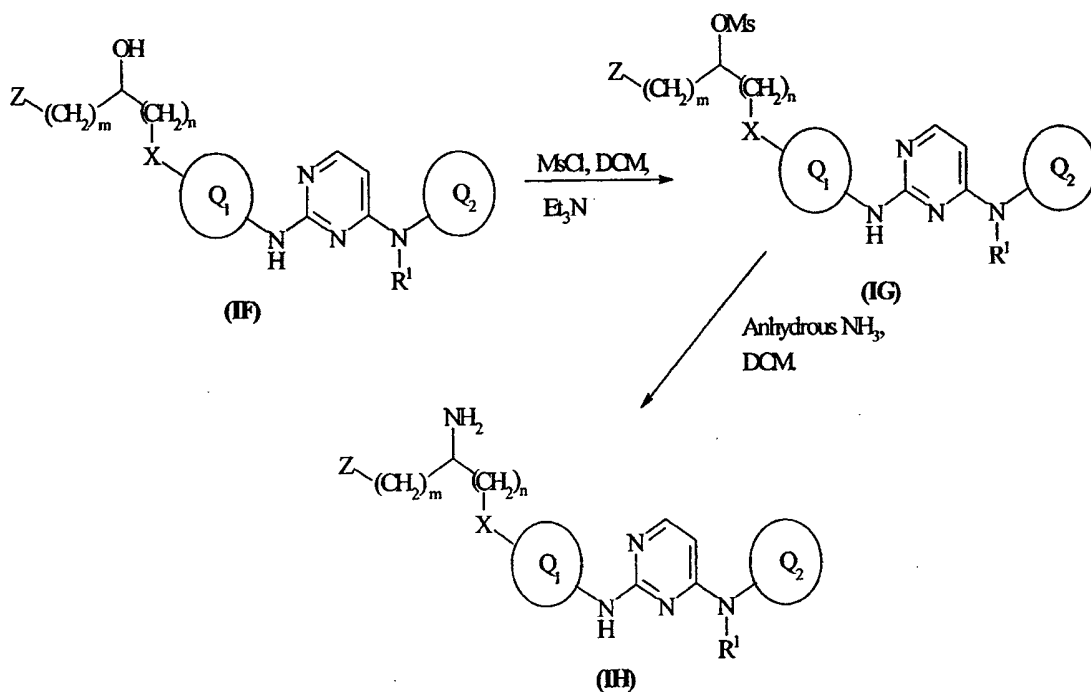
wherein Ms is methanesulphonyl, and Nu is a nucleophile that introduces a substituent that is an optional substituent for R¹ as defined in formula (I), such as Nu is -NH₂, -NHC₁₋₄alkyl, -N(C₁₋₄alkyl)₂ or -CN (NB the hydroxyl moiety does not necessarily have to be on the terminal carbon as depicted above);

- 5 Conversion iii): conversion of one side chain of formula (IA) into another side chain of formula (IA), for example:

Example I)

for compounds of formula (I) where Y is NH₂ (depicted below using ammonia), (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8)cycloalkyl,

- 10 pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino;

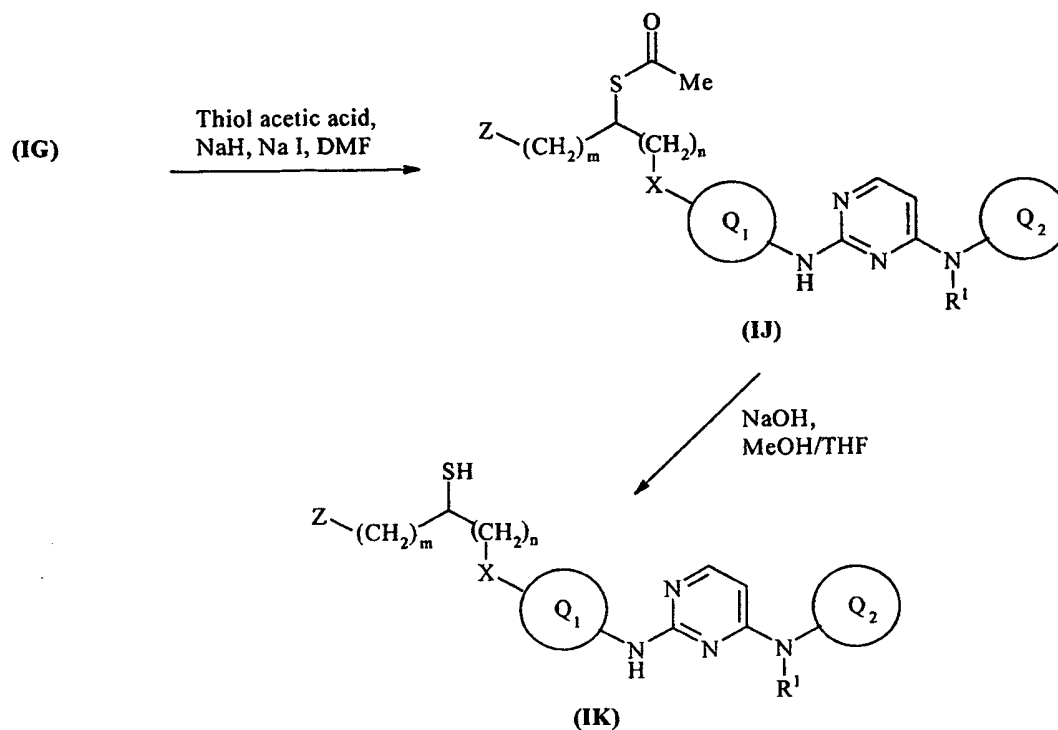


or:

Example II)

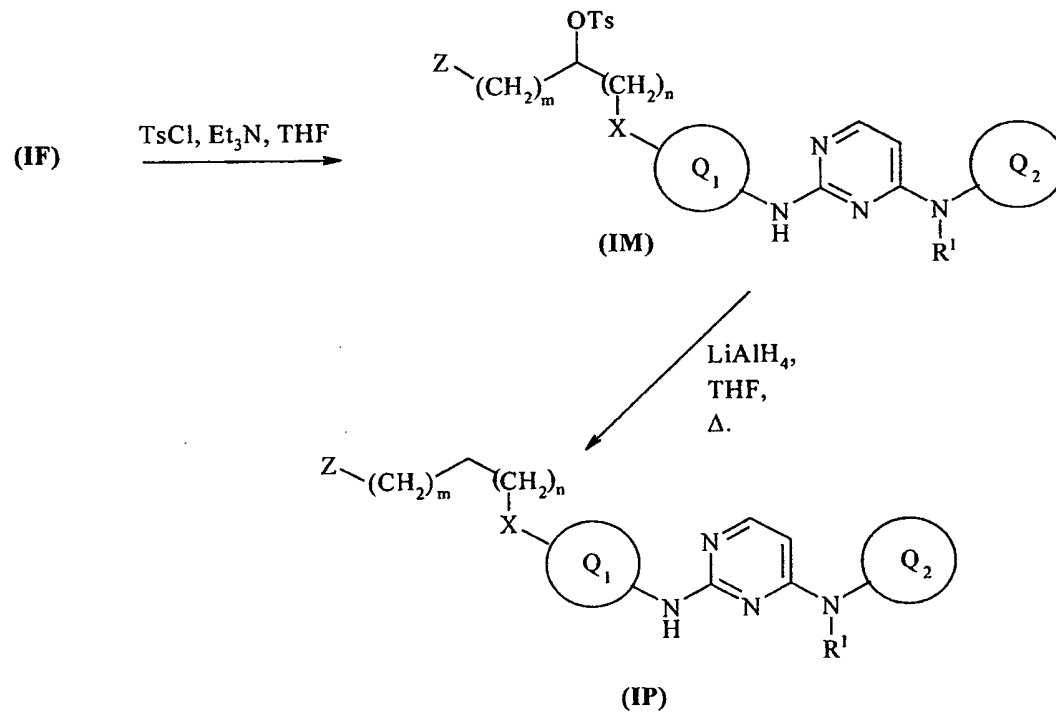
for compounds of formula (I) where Y is S:

- 32 -



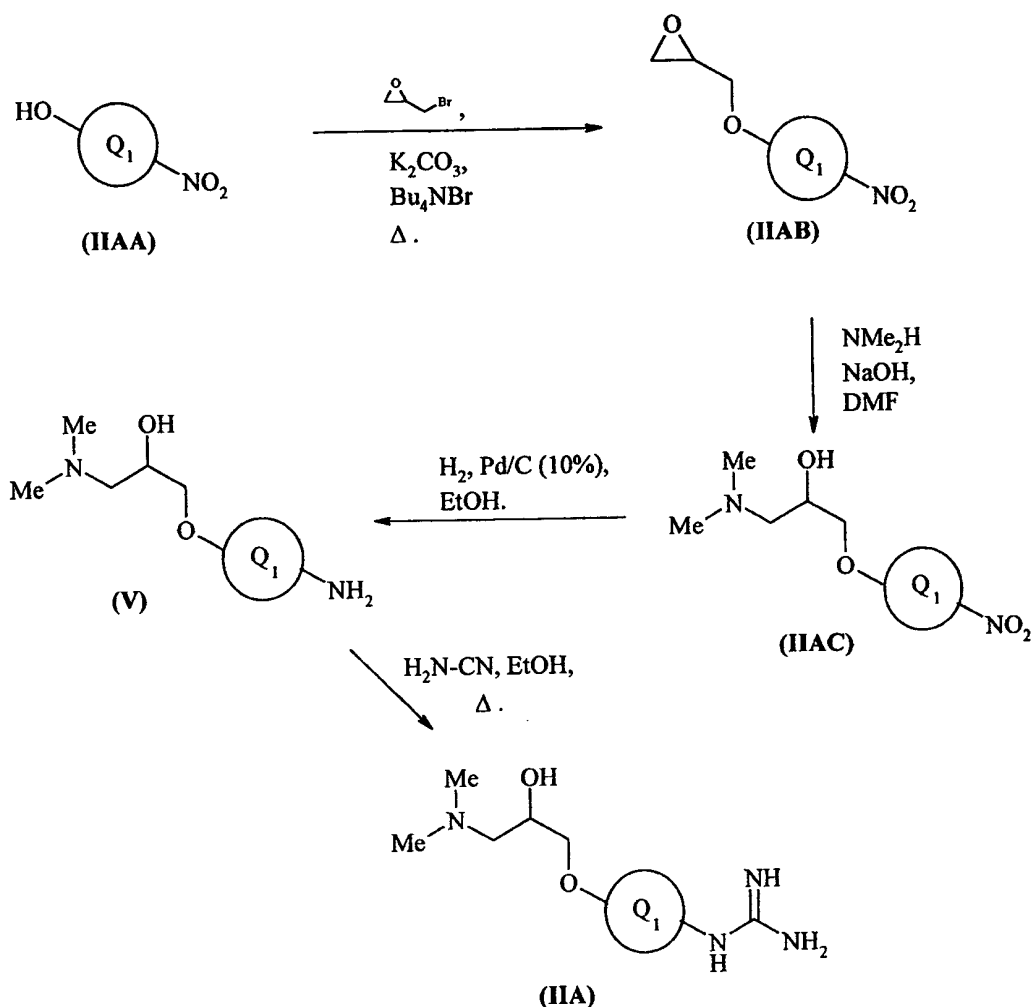
Example III)

for compounds of formula (I) where Y is H:



5 The skilled reader will appreciate that the manipulation of the side chain (IA) described in Processes c), d), e), f), g) and h) and Conversion iii) above and of the sidechain

R¹ in Conversion i) and ii) above may also be performed on intermediates, for example, to make intermediates of formula (II), (IIA), (IIB), or (V). For example:



It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group

using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl

group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

- 5 A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation
10 over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel, for example, those of the formula (II) and (IV) and these are provided as a further feature of the invention.

15 Assays

As stated hereinbefore the pyrimidine derivative defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK and/or FAK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below :-

20 CDK Inhibition Assay

The following abbreviations have been used :-

HEPES is N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]

DTT is Dithiothreitol

PMSF is Phenylmethylsulfonyl fluoride

- 25 The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ -³³P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either p16 as an inhibitor control or DMSO as a positive control.
- 30 Approximately 0.5 μ l of CDK4/Cyclin D1 partially-purified enzyme (amount dependent on enzyme activity) diluted in 25 μ l incubation buffer was added to each well then

20µl of GST-Rb/ATP/ATP33 mixture (containing 0.5µg GST-Rb and 0.2µM ATP and 0.14µCi [γ -33-P]-Adenosine Triphosphate), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150µL stop solution containing (0.8mg/well of Protein
5 A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per
10 well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM MnCl₂, 1mM DTT, 100µM Sodium vanadate, 100µM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

As a control, another known inhibitor of CDK4 may be used in place of p16.

15 Test substrate

In this assay only part of the retinoblastoma (Science 1987 Mar13;235(4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEX 2T fusion
20 vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEX 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21
25 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column
30 (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl₂, 1mM DTT, 1mM PMSF, 1ug/ml leupeptin,

1 µg/ml aprotinin and 1 µg/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

5 CDK4 and Cyclin D1

CDK4 and Cyclin D1 were cloned from RNA from MCF-7 cell line (obtained from ATCC number: HTB22, breast adenocarcinoma line) as follows. The RNA was prepared from MCF-7 cells, then reverse transcribed using oligo dT primers. PCR was used to amplify the complete coding sequence of each gene [CDK4 amino acids 1-303; Ref. Cell 1992 Oct 16; 10 71(2): 323-334; Matsushime H., Ewen M.E., Stron D.K., Kato J.Y., Hanks S.K., Roussel M.F., Sherr C.J. and Cyclin D1 amino acids 1-296; Ref. Cold Spring Harb. Symp. Quant. Biol., 1991; 56:93-97; Arnold A., Motokura T., Bloom T., Kronenburg, Ruderman J., Juppner H., Kim H.G.].

After sequencing the PCR products were cloned using standard techniques into the 15 insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number : V1392-20). The PCR products were then dually expressed [using a standard virus Baculogold co-infection technique] into the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm - commercially available).

The following Example provides details of the production of Cyclin D1/CDK4 in 20 SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin D1 & CDK4.

Example production of Cyclin D1/CDK4

SF21 cells grown in a roller bottle culture to 2.33×10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2×10^6 cells/ml. The roller bottles were incubated on a roller 25 rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86×10^6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

10 x 500ml were infected with JS303 Cyclin D1 virus titre - 9×10^7 pfu/ml. JS304 30 CDK4 virus titre - 1×10^8 pfu/ml.

$$\text{Cyclin D1} \quad \frac{1.86 \times 10^6 \times 500 \times 3}{0.9 \times 10^8} = 31 \text{ ml of virus for each 500 ml. bottle.}$$

$$\text{CDK4} \quad \frac{1.86 \times 10^6 \times 500 \times 3}{1 \times 10^8} = 28 \text{ ml of virus for each 500 ml. bottle.}$$

5

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 3 days (72 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58×10^6 cells/ml.(99% viable). The cells were spun out at 10 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 mls. lots. The supernatant was discarded.

20 pellets of $\sim 4 \times 10^8$ cells/pellet were snap frozen in LN_2 and stored at -80°C in CCRF cold room. The SF21 cells were then hypotonically lysed by resuspending in lysis buffer (50mM HEPES pH 7.5, 10mM magnesium chloride, 1mM DTT, 10mM glycerophosphate, 0.1mM PMSF, 0.1mM sodium fluoride, 0.1mM sodium orthovanadate, 15 5ug/ml aprotinin, 5ug/ml leupeptin and 20% w/v sucrose), and adding ice cold deionised water. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK4 and Cyclin D1 were coeluted with 375mM NaCl in lysis buffer, and their presence checked by western blot, using suitable anti-CDK4 and anti-Cyclin D1 antibodies (obtained from Santa Cruz Biotechnology, California, 20 US).

p16 control (Nature 366,:704-707; 1993; Serrano M, Hannon GJ, Beach D)

p16 (the natural inhibitor of CDK4/Cyclin D1) was amplified from HeLa cDNA (Hela cells obtained from ATCC CCL2, human epitheloid carcinoma from cervix; Cancer Res. 12: 25 264, 1952), cloned into pTB 375 NBSE which had a 5' His tag, and transformed using standard techniques into BL21 (DE3) pLysS cells (obtained from Promega; Ref. Studier F.W. and Moffat B.A., J. Mol. Biol., 189, 113, 1986). A 1 litre culture was grown to the appropriate OD then induced with IPTG to express p16 overnight. The cells were then lysed by sonication in 50mM sodium phoshate, 0.5M sodium chloride, PMSF, 0.5µg/mL leupeptin 30 and 0.5µg/mL aprotinin. The mixture was spun down, the supernatant added to nickel chelate

beads and mixed for 1 ½ hours. The beads were washed in sodium phosphate, NaCl pH 6.0 and p16 product eluted in sodium phosphate, NaCl pH 7.4 with 200mM imidazole.

The pTB NBSE was constructed from pTB 375 NBPE as follows :-

pTB375

5 The background vector used for generation of pTB 375 was pZEN0042 (see UK patent 2253852) and contained the tetA/tetR inducible tetracycline resistance sequence from plasmid RP4 and the cer stability sequence from plasmid pKS492 in a pAT153 derived background. pTB375 was generated by the addition of an expression cassette consisting of the T7 gene 10 promoter, multiple cloning site and T7 gene 10 termination sequence. In addition, a terminator 10 sequence designed to reduce transcriptional readthrough from the background vector was included upstream of the expression cassette.

pTB 375 NBPE

The unique EcoRI restriction site present in pTB 375 was removed. A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, 15 PstI and EcoRI was introduced into pTB 375 between the NdeI and BamHI sites destroying the original BamHI site present in pTB 375.

pTB 375 NBSE

A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, SmaI and EcoRI was introduced into pTB 375 NBPE between the 20 NdeI and EcoRI sites. The oligonucleotide containing these restriction sites also contained 6 histidine codons located between the NdeI and BamHI sites in the same reading frame as the initiator codon (ATG) present within the NdeI site.

By analogy to the above, assays designed to assess inhibition of CDK2 and CDK6 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with 25 Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

If using CDK-2 with Cyclin E partial co-purification may be achieved as follows :- Sf21 cells are resuspended in lysis buffer (50mM Tris pH 8.2, 10mM MgCl₂, 1mM DTT, 30 10mM glycerophosphate, 0.1mM sodium orthovanadate, 0.1mM NaF, 1mM PMSF, 1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce

homogeniser. After centrifugation, the supernatant is loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK-2 and Cyclin E are coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution is checked by western blot using both anti-CDK-2 and anti-
5 Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

FAK3 Kinase Inhibition Assay

This assay determines the ability of a test compound to inhibit tyrosine kinase activity of human Focal Adhesion Kinase (FAK).

- 10 DNA encoding FAK is obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These are then expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example, FAK, obtained by expression of recombinant protein in insect cells, was found to display intrinsic tyrosine kinase activity.
- 15 FAK (full length human cDNA described by Andre et al (Biochemical and Biophysical Research Communications, 1993, 190 (1): 140-147; EMBL/GenBank Accession Number L05186)) was modified such that the resulting protein when translated had a 6-histidine tag at the N-terminus immediately preceding the start methionine. Active FAK protein has been previously expressed in a baculovirus system using a similar N-terminal 6-histidine tag (Protein
20 Expression And Purification, 1996, 7: 12-18). The human FAK cDNA was cloned into the baculovirus transplacement vector, pFastbac 1 (Life Technologies), and the recombinant construct was co-transfected into insect cells (for example *Spodoptera frugiperda* 21(Sf21)) with viral DNA to prepare recombinant baculovirus (details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be
25 found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York. Details specific to the use of the pFastbac ('Bac to Bac') system are provided in Anderson et al., 1995, FOCUS (Life Technologies Bulletin Magazine), 17, p53.)
- 30 For expression of biologically active human FAK protein, Sf21 cells were infected with plaque-pure FAK recombinant virus at a multiplicity of infection of 3 and harvested 48 hours

- later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold lysis buffer (50mM HEPES pH7.5, 1mM Dithiothreitol, 100uM Sodium Fluoride, 100uM Sodium Orthovanadate, 10mM Glycerophosphate, 100uM Phenylmethylsulphonylfluoride (PMSF), 5ug/ml Aprotinin, 5ug/ml Leupeptin, 1% Tween; the PMSF being added just before use from a freshly-prepared 100mM solution in methanol) using 250ul lysis buffer per 10 million cells. The suspension was then incubated on ice for 15 minutes and centrifuged for 10 minutes at 13,000 rpm at 4°C. The supernatant (enzyme stock) was removed and aliquots made which were snap frozen in liquid nitrogen and then stored at -70°C. For a typical batch, stock enzyme was diluted 1 in 250 with enzyme diluent ((100mM HEPES pH 7.4, 0.2mM Dithiothreitol, 200uM Sodium Orthovanadate, 0.1% Triton X-100) and 50ml of freshly diluted enzyme was used for each assay well (see FAK3 protocol, below).

FAK3: In vitro Enzyme assay Protocol

- A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Maxisorp 96 well immunoplates Life technologies, Cat. No. 439454A) which were sealed with plate sealers and left overnight at 4°C.

- On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with 200ul PBST (PBS containing 0.05% v/v Tween 20) and once with 200ul 50mM Hepes pH7.4.

Test compounds were made up as 10mM or 30mM stocks in DMSO and then further diluted in glass distilled water diluted to a concentration 10 fold higher than the final assay concentration. 10µl of diluted compound was transferred to wells in the washed assay plates. "No compound" control wells contained 10ul glass distilled water instead of compound.

- Forty microlitres of 25mM manganese chloride containing 6.25µM adenosine-5'-triphosphate (ATP) was added to all test wells. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at 23C for 90 minutes. Then the reaction was stopped by adding 100ul of PBS containing 20mM EDTA. The liquid was then discarded and the wells were washed twice with PBST.

One hundred microlitres of mouse HRP-linked anti-phosphotyrosine antibody (Santa Cruz, Product SC 7020-HRP), diluted 1 in 1500 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with 200ul PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the absorbance value of the "no compound" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0.

Dose response curves were generated from the absorbance readings using Origin Software. Compounds were ranked for potency using the Inhibitory Concentration 50 (IC₅₀), as defined by Origin Software analysis.

Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) in the above assays may be demonstrated at IC₅₀ concentrations or doses in the range 250 μ M to 1nM.

When tested in the above in-vitro assays the CDK4 and FAK inhibitory activities respectively of Example 3 were measured as IC₅₀ = 0.6 μ M and IC₅₀ = 3.3 μ M; and those of Example 11 as IC₅₀ = 0.53 μ M and IC₅₀ = 3.1 μ M.

The in-vivo activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity. For example, further details may be found in the following references :-

- a) Attenuation of the Expression of the Focal Adhesion Kinase induces Apoptosis in Tumor Cells. Xu L-h et al. Cell Growth & Differentiation (1996) 7, p413-418;
- b) The COOH-Terminal Domain of the Focal Adhesion Kinase Induces Loss of Adhesion and Cell Death in Human Tumour Cells. Xu L-h et al. Cell Growth & Differentiation (1998) 9, p999-1005;
- c) Inhibition of pp125-FAK in Cultured Fibroblasts Results in Apoptosis. Hungerford J.E et al. The Journal of Cell Biology (1996) 135, p1383-1390;

d) Inhibition of Focal Adhesion Kinase (FAK) Signalling in Focal Adhesions Decreases Cell Motility and Proliferation. Gilmore A.P and Romer L.H. Molecular Biology of the Cell (1996) 7, p1209-1224.

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of protein (i.e. cells) in a well (see Boyd, M. R. (1989) Status of the NCI preclinical antitumour drug discovery screen. *Prin. Prac Oncol* 10:1-12). Thus, the following details are provided of measuring inhibition of cell growth :-

Cells were plated in appropriate medium in a volume of 100µl in 96 well plates; media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK-UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO₂) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100µl SRB dye (0.4% SRB in 1% acetic acid) was added for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC₅₀ values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular,

intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

5 The pyrimidine will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will
10 necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a pyrimidine derivative of the formula (I), or a pharmaceutically-acceptable salt or in-vivo hydrolysable
15 ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the pyrimidine derivatives defined in the present invention, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property (without being bound by theory) is
20 believed to arise from their (G1-S phase) CDK inhibitory properties. The compounds are also effective inhibitors of FAK. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK and/or FAK enzymes, i.e. the compounds may be used to produce a CDK and/or FAK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of
25 the present invention provide a method for treating the proliferation and/or migration of malignant cells characterised by inhibition of CDK and/or FAK enzymes, i.e. the compounds may be used to produce an anti-proliferative/migration effect mediated alone or in part by the inhibition of CDKs and/or FAK. The compounds may also be useful as FAK inhibitors by inducing cell-death (apoptosis). Such a pyrimidine derivative of the invention is expected to
30 possess a wide range of anti-cancer properties as CDKs and/or FAK have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach,

prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a pyrimidine derivative of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a pyrimidine derivative of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs and/or FAK, especially those tumours which are significantly dependent on CDK and/or FAK for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a pyrimidine derivative of the present invention will possess activity against other cell-proliferation/migration diseases in a wide range of other disease states including leukemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a pyrimidine derivative of the formula (I), or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a pyrimidine derivative of the formula (I), or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal such as man. Particularly, a cell cycle inhibitory effect is produced at the G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering

to said animal an effective amount of a pyrimidine derivative as defined immediately above. Particularly, an inhibitory effect is produced at the G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK and/or FAK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

- (i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and
- (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate,

fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, 5 chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a pyrimidine derivative of the formula (I) as defined 10 hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer. An anti-emetic may also be usefully administered, for example when using such conjoint treatment as described above.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development 15 and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the 20 invention described herein also apply.

Examples

The invention will now be illustrated in the following non-limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise 25 stated:-

- (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of 30 an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid

- chromatography (MPLC), for example using an Anachem Sympur MPLC, were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany; where a Mega Bond Elut column is referred to, this means a column containing 10 g or 20 g of silica of 40 micron particle size, the silica being contained in a 60 ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; "Mega Bond Elut" is a trademark;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured in deuterated DMSO (unless otherwise stated); at ambient temperature unless marked 373K; on the delta scale (ppm downfield from tetramethylsilane); using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz or a Bruker DPX400 spectrometer operating at a field strength of 400 MHz; and peak multilicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; mass spectrometry (MS) was performed by electrospray on a VG platform;
- (vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), infra-red (IR), MS or NMR analysis;
- (vii) it is to be understood that in this Examples section certain symbols, such as R₁ and R₂, have been used to describe certain Examples in Tables, and that the use of such symbols should be read in context with the Examples to which they refer;
- (viii) certain geometric isomers (such as shown in Examples 38 & 42) may exist as E- and Z-isomers; it is to be understood that where one isomer, or no particular isomer, is shown this refers to a mixture of both isomers;
- (ix) the following abbreviations may be used hereinbefore or hereinafter :-

DMF	N,N-dimethylformamide;
CDCl ₃	deuterated chloroform;
MeOH-δ ₄	deuterated methanol;
EA	elemental analysis;
NMP	1-methyl-2-pyrrolidinone;

	DEAD	diethyl azodicarboxylate;
	DTAD	diterbutyl azodicarboxylate;
	EtOH	ethanol;
	DIPEA	diisopropylethylamine;
5	DCM	dichloromethane;
	TFA	trifluoroacetic acid;
	EtOAc	ethyl acetate; and
	DMSO	dimethylsulphoxide.

10 **Example 1**

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(2,5-dimethylanilino)pyrimidine

2-Chloro-4-(2,5-dimethylanilino)pyrimidine (Reference Example A-1; 250 mg, 1.07 mmol) was dissolved in *n*-butanol (5 ml) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy] aniline hydrochloride (Reference Example D-1; 295 mg, 1.07 mmol) was added. The resulting
15 suspension was treated with methanol until all the solid dissolved. The reaction mixture was heated at 100°C for 8 hours and allowed to cool to ambient temperature. The reaction mixture was then basified to pH 9-10 using methanolic ammonia and then evaporated onto silica (5 ml). The residue was purified by column chromatography eluting with methanol (15%):DCM:aqueous ammonia (1%). The resulting gum was recrystallized from acetonitrile
20 to give the title product as a solid (104 mg, 24%). NMR (300 MHz): 2.13 (s, 3H), 2.25 (s, 3H), 2.79 (s, 6H), 3.19 (m, 2H), 3.88 (m, 2H), 4.21 (m, 1H), 5.88 (brs, 1H), 6.05 (d, 1H), 6.73 (d, 2H), 6.93 (d, 1H), 7.12 (d, 1H), 7.26 (s, 1H), 7.55 (d, 2H), 7.9 (d, 1H), 8.6 (s, 1H), 8.88 (s, 1H); *m/z*: (ES⁺) 408.4 (MH⁺).

25 **Method A: Displacement of 4-chloro from 2,4-dichloropyrimidine by an aniline**

Reference Example A-1

2-Chloro-4-(2,5-dimethylanilino)pyrimidine

2,4-Dichloropyrimidine (500 mg, 3.36 mmol), 2,5-dimethylaniline (407 mg, 3.36 mmol) and triethylamine (0.51 ml, 3.69 mmol) were dissolved in EtOH (5 ml) with stirring.
30 The reaction mixture was heated at reflux for 12 hours, cooled and evaporated onto silica (5 ml). The residue was purified by column chromatography and eluted with EtOAc (30%) :

isohexane to give the title product as a waxy solid on evaporation (514 mg, 66%). NMR (300 MHz): 2.1 (s, 3H), 2.27 (s, 3H), 6.42 (d, 1H), 6.99 (d, 1H), 7.08 (s, 1H), 7.18 (d, 1H), 8.03 (d, 1H), 9.45 (s, 1H); m/z: (ES⁺) 234.3 (MH⁺).

5 **Example 2**

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(2,4-difluoroanilino)pyrimidine

2-Chloro-4-(2,4-difluoroanilino)pyrimidine (Reference Example A-2; 174 mg, 0.72 mmol) was dissolved in *n*-butanol (2 ml) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy] aniline hydrochloride (Reference Example D-1; 198 mg, 0.72 mmol) was added. The resulting
10 suspension was treated with methanol until all the solid dissolved. The reaction mixture was heated at 100°C for 12 hours and allowed to cool to ambient temperature. The reaction mixture was then basified to pH 9-10 using methanolic ammonia and evaporated onto silica (5 ml). The residue was purified by column chromatography eluting with methanol (15%) : DCM:aqueous ammonia(1%). The resulting gum was recrystallized from acetonitrile to give
15 the title product as a solid (124 mg, 41%). NMR (300 MHz): 2.18 (s, 6H), 2.34 (m, 2H), 3.78 (m, 1H), 3.88 (m, 2H), 4.75 (brd, 1H), 6.18 (d, 1H), 6.75 (d, 2H), 7.03 (t, 1H), 7.32 (t, 1H), 7.48 (d, 2H), 7.88 (dd, 1H), 7.95 (d, 1H), 8.88 (s, 1H), 8.95(s, 1H); m/z: (ES⁺) 416.4 (MH⁺).

Reference Example A-2

20 2-Chloro-4-(2,4-difluoroanilino)pyrimidine

2,4-Dichloropyrimidine (200 mg, 1.34 mmol), 2,4-difluoroaniline (173 mg, 1.34 mmol) and diisopropylethylamine (0.26 ml, 1.48 mmol) were dissolved in *n*-butanol (5 ml). The reaction mixture was heated at reflux for 12 hours, cooled and evaporated onto silica (5 ml). The residue was purified by column chromatography and eluted with EtOAc (30%) :
25 isohexane to give the title product as a solid on evaporation (174 mg, 54%). NMR (300 MHz): 6.70 (d, 1H), 7.12 (t, 1H), 7.38 (t, 1H), 7.70 (dd, 1H), 8.14 (d, 1H), 9.74 (brs, 1H); m/z: (ES⁺) 242.1 (MH⁺).

Method B: Formation of 4-(nitrophenoxy)epoxyalkyls.**Reference Example B-1****1-(4-Nitrophenoxy)-2,3-epoxypropane**

1-(4-Nitrophenoxy)-2,3-epoxypropane was prepared by an analogous method to that
5 described by Zhen-Zhong Lui *et. al.* in Synthetic Communications (1994), 24, 833-838.

4-Nitrophenol (4.0 g), anhydrous potassium carbonate (8.0 g) and
tetrabutylammonium bromide (0.4 g) were mixed with epibromohydrin (10 ml). The reaction
mixture was heated at 100°C for 1 hour. After cooling to ambient temperature, the reaction
mixture was diluted with EtOAc and filtered. The filtrate was evaporated to dryness and the
10 residue was co-distilled twice with toluene. The resulting oil was purified by column
chromatography and eluted with EtOH (1.0%):DCM to give the title product on evaporation
as an oil that crystallised (4.36 g, 77.7%). NMR (CDCl₃, 300 MHz): 2.78 (m, 1H), 2.95 (m,
1H), 3.38 (m, 1H), 4.02 (dd, 1 H), 4.38 (dd, 1H), 7.00 (d, 2H), 8.20 (d, 2H); m/z: (ES⁺) 196
(MH⁺).

15

Method C: Epoxide opening reactions.**Reference Example C-1****3-(N,N-Dimethyl)amino-2-hydroxy-1-(4-nitrophenoxy)propane**

1-(4-Nitrophenoxy)-2,3-epoxypropane (Reference Example B-1, 4.3 g) was dissolved
20 in methanol (30 ml) and DMF (10 ml). Dimethylamine (2M solution in methanol, 17 ml) was
added and the mixture was stirred at ambient temperature overnight. The reaction mixture was
evaporated to dryness and the residue was dissolved in saturated sodium bicarbonate solution
and EtOAc. The EtOAc layer was separated and washed twice with saturated brine, dried over
anhydrous sodium sulphate, filtered and evaporated to give the title product as an oil that
25 slowly crystallised under high vacuum (4.79 g, 89.9%). NMR (CDCl₃, 300 MHz): 2.33 (s,
6H), 2.98 (m, 1H), 2.54 (m, 1H), 4.00 (m, 3 H), 7.00 (d, 2H), 8.20 (d, 2H); m/z: (ES⁺) 241
(MH⁺).

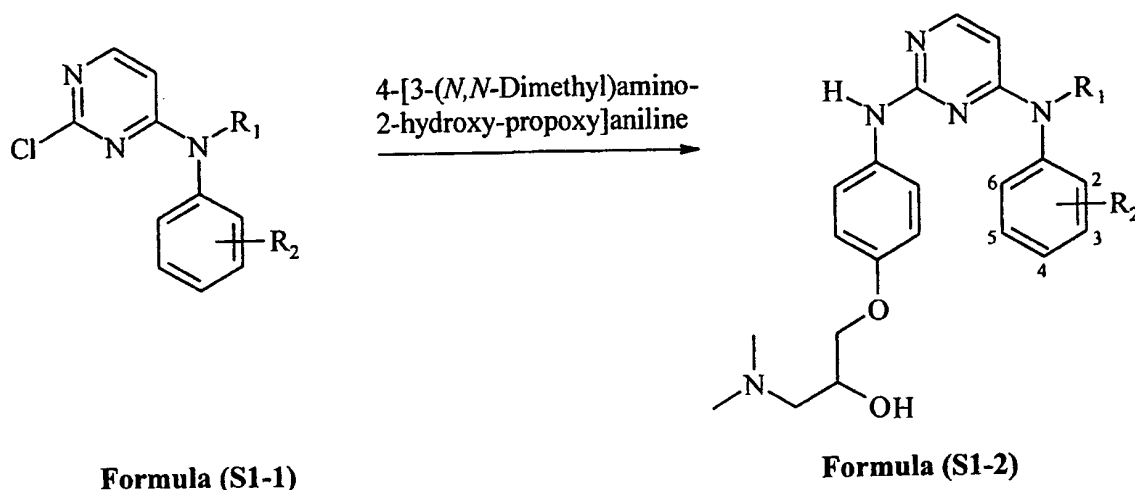
Method D: Reduction of aromatic nitro moiety.**Reference Example D-1****4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]aniline**

3-(*N,N*-Dimethyl)amino-2-hydroxy-3-(4-nitrophenoxy)propane (Reference Example
5 C-1, 3.75 g) was dissolved in EtOH (40 ml). Under an atmosphere of nitrogen, 10%
palladium-on-carbon (0.4 g) was added. The nitrogen atmosphere was replaced by one of
hydrogen and the reaction mixture was stirred overnight. The catalyst was removed by
filtration through diatomaceous earth and the filtrate was evaporated to dryness. The residue
was dissolved in diethyl ether containing a small amount of isopropanol and hydrogen
10 chloride solution (1M in ether, 16 ml) was added. The ether was evaporated and the solid
residue was suspended in isopropanol. This mixture was heated on a steam bath for several
minutes then allowed to cool to ambient temperature. The resulting powder was collected by
filtration, washed with isopropanol, ether and dried to give the title product (3.04 g, 72.4%).
NMR (300 MHz): 2.80 (s, 6H), 3.15 (m, 2H), 3.88 (m, 2H), 4.25 (m, 1H), 5.93 (br S, 1H),
15 6.88 (m, 4H); m/z: (ES⁺) 211 (MH⁺); EA: C₁₁H₁₈N₂O₂·1.6 HCl requires C; 49.2, H; 7.4, N;
10.4, Cl; 21.7%; found: C; 49.2, H; 7.2, N; 10.1; Cl; 19.1%.

Examples 3-11

Examples 3-11 of Formula (S1-2) were prepared by the method of Example 2
20 according to Scheme 1 below. They were prepared using 4-[3-(*N,N*-dimethyl)amino-2-
hydroxypropoxy]aniline (Reference Example D-1) and the appropriate 2-chloro-4-
anilinopyrimidine of Formula (S1-1). These 2-chloro-4-anilinopyrimidines starting materials
of Formula (S1-1) are either commercially available or are readily prepared by standard
methods from known materials (by analogy to Method A and the corresponding Reference
25 Examples A-1 - A-10).

- 53 -



Scheme 1

Ex No	R ₁	R ₂	NMR (300 MHz)	m/z (MH ⁺)
3	H	2-Br-4-CH ₃	2.20 (s, 6H), 2.38 (m, 5H), 3.77 (m, 1H), 3.88 (m, 2H), 4.79 (s, 1H), 6.09 (d, 1H), 6.7 (d, 2H), 7.19 (d, 1H), 7.49 (m, 4H), 7.93 (d, 1H), 8.67 (s, 1H), 8.80 (s, 1H).	472.4
4	H	2-CH ₃ -5-F	2.19 (s, 3H), 2.40 (s, 6H), 2.66 (m, 2H), 3.82 (m, 2H), 3.99 (m, 1H), 6.20 (d, 1H), 6.74 (d, 2H), 6.88 (t, 1H), 7.22 (t, 1H), 7.52 (d, 2H), 7.56 (dd, 1H), 7.97 (d, 1H), 8.59 (s, 1H), 8.90 (s, 1H).	412.4
5	CH ₂ CH ₂ OH	2-CH ₃	(373K): 2.09 (s, 3H), 2.20 (s, 6H), 2.38 (m, 2H), 3.66 (m, 2H), 3.89 (m, 5H), 4.30 (s, 2H), 5.43 (d, 1H), 6.78 (d, 2H), 7.30 (m, 4H), 7.50 (d, 2H), 7.79 (d, 1H), 8.41 (s, 1H).	438.5
6	H	4-Cl	2.19 (s, 6H), 2.33 (m, 2H), 3.86 (m, 3H), 4.76 (d, 1H), 6.14 (d, 1H), 6.85 (d, 2H), 7.29 (d, 2H), 7.54 (d, 2H), 7.73 (d, 2H), 7.98 (d, 1H), 8.94 (s, 1H), 9.39 (s, 1H).	414.5

7	H	4-OCH ₃	2.17 (s, 6H), 2.32 (m, 2H), 3.71 (s, 3H), 3.83 (m, 3H), 4.72 (d, 1H), 6.06 (d, 1H), 6.80 (d, 2H), 6.87 (d, 2H), 7.55 (t, 4H), 7.89 (d, 1H), 8.81 (s, 1H), 9.03 (s, 1H).	410.5
8	H	4-CH ₃	2.18 (s, 6H), 2.24 (s, 3H), 2.33 (m, 2H), 3.83 (m, 3H), 4.74 (d, 1H), 6.10 (d, 1H), 6.81 (d, 2H), 7.08 (d, 2H), 7.55 (t, 4H), 7.92 (d, 1H), 8.84 (s, 1H), 9.12 (s, 1H).	394.5
9	H	3,4-diCl	2.18 (s, 6H), 2.32 (m, 2H), 3.85 (m, 3H), 4.75 (d, 1H), 6.15 (d, 1H), 6.85 (d, 2H), 7.50 (m, 4H), 8.00 (d, 1H), 8.11 (d, 1H), 9.02 (s, 1H), 9.53 (s, 1H).	448.4
10	H	3-Cl	2.16 (s, 6H), 2.31 (m, 2H), 3.83 (m, 3H), 4.73 (d, 1H), 6.15 (d, 1H), 6.83 (d, 2H), 6.99 (d, 1H), 7.28 (t, 1H), 7.52 (d, 3H), 7.89 (s, 1H), 7.99 (d, 1H), 8.99 (s, 1H), 9.42 (s, 1H).	414.4
11	H	2,5-diCl	2.17 (s, 6H), 2.30 (m, 2H), 3.76 (m, 1H), 3.86 (m, 2H), 4.72 (d, 1H), 6.35 (d, 1H), 6.77 (d, 2H), 7.19 (dd, 1H), 7.47 (d, 2H), 7.52 (d, 1H), 8.01 (d, 2H), 8.88 (s, 1H), 8.99 (s, 1H).	448.4

Example 12

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(*N*-(*n*-butyl)anilino)pyrimidine

2-Chloro-4-(*N*-(*n*-butyl)anilino)pyrimidine (570 mg, 2.18 mmol) was dissolved in *n*-butanol (4 ml) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline dihydrochloride (Reference Example D-1; 554 mg, 1.97 mmol) was added. The resulting suspension was treated with methanol until all the solid dissolved. The reaction mixture was heated at 95°C for 12 hours and allowed to cool to ambient temperature. The reaction mixture was then basified to pH 9-10 using methanolic ammonia and then evaporated onto silica (5 ml). The residue was purified by column chromatography eluting with methanol (15%) : DCM : aqueous ammonia (1%). The resulting gum was re-evaporated from EtOAc twice to give the title product as a foam (130 mg).

NMR: (353K, 400 MHz) 0.86 (t, 3H), 1.31 (m, 2H), 1.59 (m, 2H), 2.88 (s, 6H), 3.22 (m, 1H), 3.32 (dd, 1H), 3.94 (m, 2H), 4.00 (m, 2H), 4.34 (m, 1H), 5.85 (d, 1H), 6.98 (d, 2H), 7.38 (d, 2H), 7.49 (m, 3H), 7.58 (m, 2H), 7.89 (d, 1H), 10.47 (s, 1H); M.S.: (ES⁺) 436.5 (MH⁺).

5 **Example 13**

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(*N*-(carbamoylmethyl)anilino)pyrimidine

2-Chloro-4-(*N*-(carbamoylmethyl)anilino)pyrimidine (prepared by analogy to Method A and the corresponding Reference Examples A-1 - A-10) (390 mg, 1.49 mmol) was dissolved in NMP (3 ml) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline dihydrochloride (Reference Example D-1; 378 mg, 1.34 mmol) was added. The resulting suspension was heated at 120°C which caused the solid to dissolve. The reaction mixture was heated at 120°C for 12 hours and allowed to cool to ambient temperature. The reaction mixture was then basified to pH 9-10 using methanolic ammonia and then evaporated onto silica (5 ml). The residue was purified by column chromatography eluting with methanol (15%) : DCM : aqueous ammonia (1%). The resulting gum was re-evaporated from EtOAc three times to give the title product as a foam (184 mg). NMR: (300 MHz) 2.31 (s, 6H), 2.49 (m, 2H), 3.8 (m, 1H), 3.92 (m, 2H), 4.42 (s, 2H), 5.68 (d, 1H), 6.79 (d, 2H), 7.4 (m, 5H), 7.58 (d, 2H), 7.82 (d, 1H), 8.93 (s, 1H); m/z: (ES⁺) 437.5 (MH⁺).


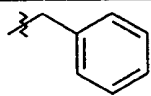

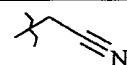
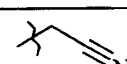


20

Examples 14-46

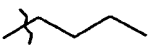

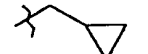
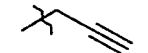
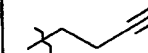
Examples 14-45 of Formula (S1-2) were prepared by the method of Example 12, and Example 46 by the method of Example 13, according to Scheme 1, using 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline (Reference Example D-1) and the appropriate 2-chloro-4-(*N*-alkylated)anilinopyrimidine intermediate of Formula (S1-1), (or, for Example 18, 2-chloro-4-[indan-5-yl(*N*-cyanomethyl)amino]pyrimidine). These 2-chloro-4-(*N*-alkylated)anilinopyrimidine intermediates of Formula (S1-1) were prepared according to Scheme 2 by analogy to Method E described below, using the appropriate 2-chloro-4-anilinopyrimidine intermediate (prepared by analogy to Method A and the corresponding Reference Examples A-1 - A-10) and the appropriate alkylating agent.

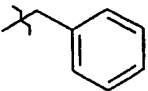
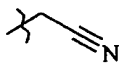
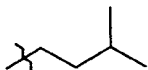
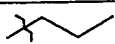
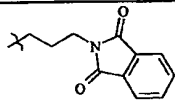
30

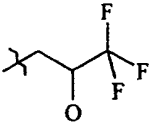
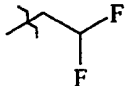

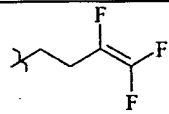
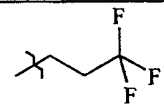
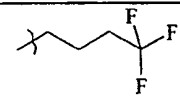
For Example 18, the appropriate intermediate was prepared by analogy with Example 70, followed by N-alkylation with Cl-CH₂-CN.

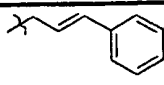
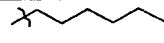
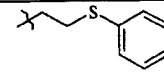
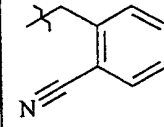
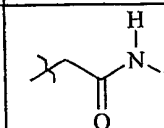
Ex No	R ₁	R ₂	NMR 300 MHz	m/z (MH ⁺)
14		H	0.02 (m, 2H), 0.31 (m, 2H), 0.99 (m, 1H), 2.71 (s, 6H), 3.12 (m, 2H), 3.71 (d, 2H), 3.81 (m, 2H), 4.18 (m, 1H), 5.48 (d, 1H), 5.81 (d, 1H), 6.75 (d, 2H), 7.28 (m, 3H), 7.41 (m, 2H), 7.51 (d, 2H), 7.70 (d, 1H), 8.86 (s, 1H).	434.5
15		H	2.72 (s, 6H), 3.08 (m, 2H), 3.86 (d, 2H), 4.17 (m, 1H), 5.19 (s, 2H), 5.72 (d, 2H), 6.71 (d, 2H), 7.28 (m, 8H), 7.44 (m, 4H), 7.86 (d, 1H), 8.98 (s, 1H).	470.5
16		H	2.82 (s, 6H), 2.89 (m, 2H), 3.21 (m, 2H), 3.91 (m, 2H), 4.14 (t, 2H), 4.28 (m, 1H), 5.66 (d, 1H), 5.97 (d, 1H), 6.90 (d, 2H), 7.37 (d, 2H), 7.42 (m, 1H), 7.54 (m, 4H), 7.86 (d, 1H), 9.47 (brs, 1H).	433.5
17		H	2.21 (s, 6H), 2.36 (m, 2H), 3.80 (m, 1H), 3.90 (m, 2H), 4.86 (brs, 1H), 4.95 (s, 2H), 5.71 (d, 1H), 6.83 (d, 2H), 7.38 (d, 2H), 7.44 (m, 1H), 7.58 (m, 4H), 7.96 (d, 1H), 9.23 (s, 1H).	419.5
18		 So that Q2 is 	2.8 (m, 2H), 2.82 (brs, 6H), 2.91 (t, 4H), 3.22 (m, 2H), 3.92 (m, 2H), 4.25 (m, 1H), 4.89 (s, 2H), 5.69 (d, 1H), 5.93 (d, 1H), 6.88 (d, 2H), 7.09 (dd, 1H), 7.20 (s, 1H), 7.38 (d, 1H), 7.63 (d, 2H), 7.92 (d, 1H), 9.27 (s, 1H).	459.5

19		4-Cl	2.62 (s, 6H), 2.95 (m, 2H), 3.89 (d, 2H), 4.13 (m, 1H), 4.93 (s, 2H), 5.79 (d, 1H), 6.84 (d, 2H), 7.40 (d, 2H), 7.60 (m, 4H), 7.98 (d, 1H), 9.22 (s, 1H).	453.4
20		2,4-diF	2.62 (s, 6H), 2.95 (m, 2H), 3.88 (d, 2H), 4.13 (m, 1H), 4.91 (s, 2H), 5.79 (brd, 1H), 6.83 (d, 2H), 7.28 (t, 1H), 7.54 (m, 4H), 8.01 (d, 1H), 9.23 (s, 1H).	455.5
21		3,4-diCl	2.60 (s, 6H), 2.92 (m, 2H), 3.89 (d, 2H), 4.12 (m, 1H), 4.97 (s, 2H), 5.92 (d, 1H), 6.83 (d, 2H), 7.40 (dd, 1H), 7.57 (d, 2H), 7.73 (s, 1H), 7.80 (d, 1H), 8.01 (d, 1H), 9.24 (s, 1H).	487.4
22		H	2.88 (s, 6H), 3.22 (m, 1H), 3.31 (dd, 1H), 4.00 (m, 2H), 4.26 (m, 2H), 4.32 (m, 1H), 4.62 (m, 1H), 4.73 (m, 1H), 5.81 (d, 1H), 6.93 (d, 2H), 7.38 (d, 2H), 7.49 (m, 3H), 7.56 (m, 2H), 7.89 (d, 1H), 9.78 (brs, 1H).	426.5
23		H	2.88 (s, 6H), 3.22 (m, 2H), 3.33 (dd, 1H), 4.01 (m, 2H), 4.33 (m, 1H), 4.76 (s, 2H), 5.93 (d, 1H), 6.97 (d, 2H), 7.42 (d, 2H), 7.55 (m, 5H), 7.96 (d, 1H), 10.33 (s, 1H).	418.4
24		2-Br-4-CH ₃	2.41 (s, 3H), 2.74 (s, 6H), 3.08 (m, 2H), 3.98 (m, 2H), 4.22 (m, 1H), 4.86 (brs, 2H), 5.57 (d, 1H), 6.89 (d, 2H), 7.39 (s, 2H), 7.61 (d, 2H), 7.69 (s, 1H), 7.98 (d, 1H), 8.81 (brs, 1H).	511.5
25		2-Cl-5-CH ₃	2.39 (s, 3H), 2.76 (s, 6H), 3.06 (m, 1H), 3.17 (dd, 1H), 3.97 (m, 2H), 4.23 (m, 1H), 4.88 (s, 2H), 5.61 (d, 1H), 6.90 (d, 2H), 7.34 (m, 2H), 7.56 (d, 1H), 7.61 (d, 2H), 8.00 (d, 1H), 8.80 (s, 1H).	467.5

26		2,5-diCl	0.89 (t, 3H), 1.36 (m, 2H), 1.63 (m, 2H), 2.89 (s, 6H), 3.21 (m, 1H), 3.32 (dd, 1H), 3.85 (m, 2H), 4.00 (m, 2H), 4.34 (m, 1H), 5.96 (brs, 1H), 6.89 (d, 2H), 7.40 (d, 2H), 7.60 (dd, 1H), 7.62 (s, 1H), 7.71 (d, 1H), 8.00 (d, 1H), 9.91 (brs, 1H).	504.5
27		2,5-diCl	2.88 (s, 6H), 3.21 (m, 1H), 3.31 (dd, 1H), 3.99 (m, 2H), 4.19 (brd, 2H), 4.33 (m, 1H), 4.62 (m, 1H), 4.73 (m, 1H), 5.93 (brs, 1H), 6.88 (d, 2H), 7.42 (d, 2H), 7.58 (dd, 1H), 7.63 (s, 1H), 7.71 (d, 1H), 8.00 (d, 1H), 9.62 (brs, 1H).	494.4
28		2,5-diCl	0.00 (m, 2H), 0.31 (m, 2H), 0.89 (m, 1H), 2.71 (s, 6H), 3.06 (m, 1H), 3.17 (dd, 1H), 3.63 (brd, 2H), 3.83 (m, 2H), 4.18 (m, 1H), 5.80 (brs, 1H), 6.74 (d, 2H), 7.22 (d, 2H), 7.43 (dd, 1H), 7.49 (s, 1H), 7.55 (d, 1H), 7.83 (d, 1H), 9.81 (brs, 1H).	502.4
29		2,5-diCl	2.70 (s, 6H), 2.98 (s, 1H), 3.04 (m, 1H), 3.17 (dd, 1H), 3.84 (m, 2H), 4.17 (m, 1H), 4.54 (s, 2H), 5.79 (d, 1H), 6.71 (d, 2H), 7.29 (d, 2H), 7.43 (dd, 1H), 7.46 (s, 1H), 7.56 (d, 1H), 7.89 (d, 1H), 9.50 (brs, 1H).	486.4
30		2,5-diCl	2.86 (s, 6H), 2.96 (m, 2H), 3.19 (m, 1H), 3.29 (dd, 1H), 3.98 (m, 2H), 4.09 (m, 2H), 4.28 (m, 1H), 5.66 (d, 1H), 6.87 (d, 2H), 7.54 (d, 2H), 7.58 (dd, 1H), 7.66 (s, 1H), 7.70 (d, 1H), 7.98 (d, 1H), 8.73 (s, 1H).	501.4

31		2,5-diCl	2.79 (s, 6H), 3.13 (m, 1H), 3.24 (dd, 1H), 3.90 (m, 2H), 4.24 (m, 1H), 5.06 (brs, 2H), 5.90 (brd, 1H), 6.78 (d, 2H), 7.23 (m, 5H), 7.31 (m, 3H), 7.44 (dd, 1H), 7.58 (d, 1H), 7.97 (d, 1H), 9.69 (brs, 1H).	538.5
32		2,5-diCl	2.79 (s, 6H), 3.09 (m, 1H), 3.20 (dd, 1H), 3.98 (m, 2H), 4.25 (m, 1H), 4.91 (s, 2H), 5.74 (d, 1H), 6.88 (d, 2H), 7.58 (d, 2H), 7.60 (dd, 1H), 7.63 (s, 1H), 7.73 (d, 1H), 8.04 (d, 1H), 8.85 (brs, 1H).	487.4
33		2,5-diCl	0.89 (d, 6H), 1.53 (m, 2H), 1.62 (m, 1H), 2.89 (s, 6H), 3.23 (m, 1H), 3.34 (dd, 1H), 3.87 (m, 2H), 4.00 (m, 2H), 4.34 (m, 1H), 5.88 (d, 1H), 6.89 (d, 2H), 7.40 (d, 2H), 7.59 (dd, 1H), 7.62 (s, 1H), 7.71 (d, 1H), 7.99 (d, 1H), 9.75 (brs, 1H).	518.5
34		2,5-diCl	0.93 (t, 3H), 1.68 (m, 2H), 2.89 (s, 6H), 3.21 (m, 1H), 3.32 (dd, 1H), 3.81 (m, 2H), 4.00 (m, 2H), 4.33 (m, 1H), 5.96 (d, 1H), 6.88 (d, 2H), 7.39 (d, 2H), 7.59 (dd, 1H), 7.61 (s, 1H), 7.70 (d, 1H), 7.99 (d, 1H), 9.89 (brs, 1H).	490.4
35		2,5-diCl	1.85 (m, 2H), 2.72 (s, 6H), 3.06 (m, 1H), 3.18 (dd, 1H), 3.52 (t, 2H), 3.80 (m, 2H), 3.86 (m, 2H), 4.18 (m, 1H), 5.73 (brd, 1H), 6.73 (d, 2H), 7.27 (d, 2H), 7.39 (dd, 1H), 7.48 (s, 1H), 7.50 (d, 1H), 7.68 (s, 4H), 7.83 (d, 1H), 9.39 (brs, 1H).	635.5

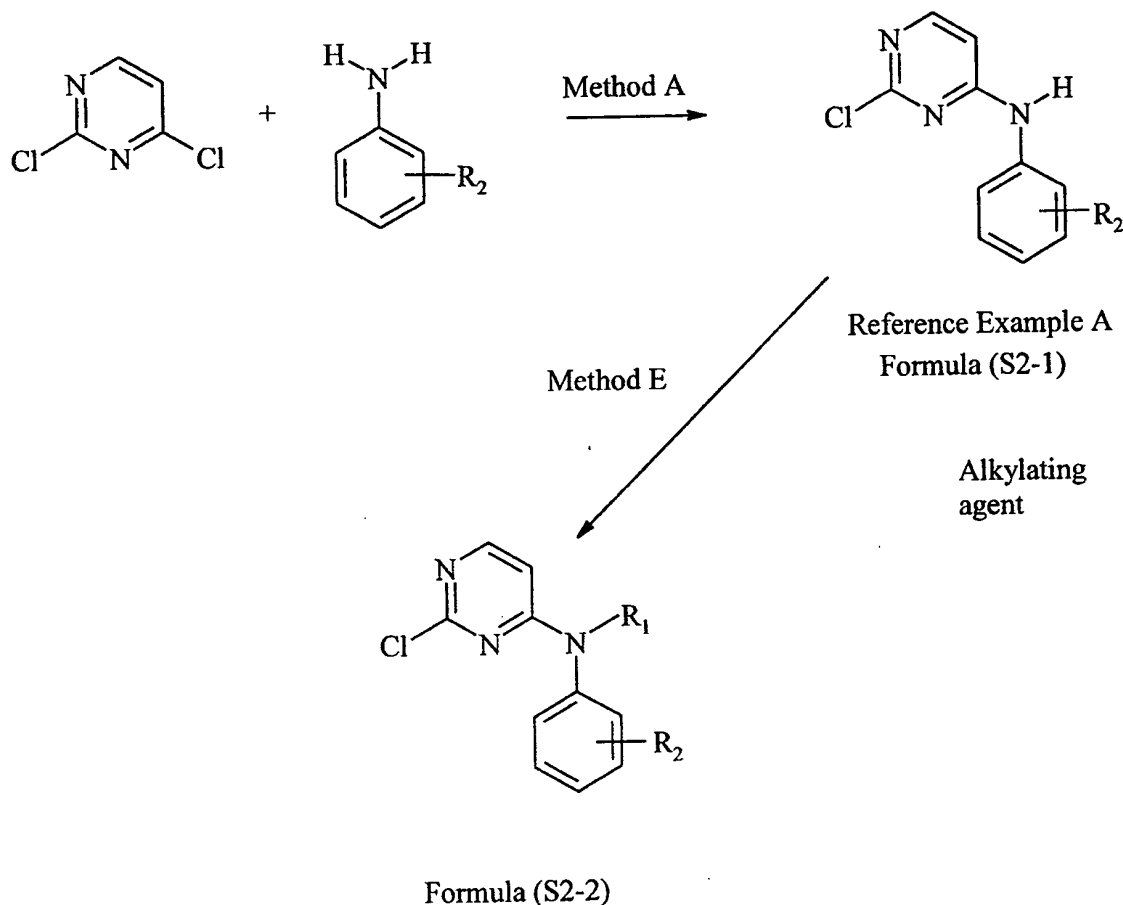
36		2,5-diCl	2.86 (s, 6H), 3.19 (m, 1H), 3.30 (dd, 1H), 3.98 (m, 2H), 4.30 (m, 2H), 4.48 (m, 1H), 5.63 (d, 1H), 6.83 (d, 2H), 7.51 (m, 3H), 7.67 (d, 1H), 7.69 (s, 1H), 7.95 (d, 1H), 8.72 (brs, 1H).	560.4
37		2,5-diCl	2.89 (s, 6H), 3.21 (m, 1H), 3.32 (dd, 1H), 3.97 (m, 2H), 4.29 (m, 3H), 5.79 (s, 1H), 6.34 (brt, 1H), 6.88 (d, 2H), 7.48 (d, 2H), 7.59 (d, 1H), 7.62 (s, 1H), 7.70 (d, 1H), 8.00 (d, 1H), 9.28 (brs, 1H).	512.4
38		2,5-diCl	2.78 (s, 6H), 3.08 (m, 1H), 3.19 (dd, 1H), 3.95 (m, 2H), 4.24 (m, 1H), 4.52 (brdd, 2H), 5.70 (d, 1H), 6.48 (m, 1H), 6.59 (d, 1H), 6.82 (d, 2H), 7.52 (m, 4H), 7.68 (d, 1H), 7.97 (d, 1H), 8.66 (brs, 1H).	566.4
39		2,5-diCl	2.79 (m, 2H), 2.89 (s, 6H), 3.21 (m, 1H), 3.30 (dd, 1H), 3.98 (m, 2H), 4.09 (m, 2H), 4.31 (m, 1H), 5.86 (brs, 1H), 6.89 (d, 2H), 7.42 (d, 2H), 7.62 (m, 2H), 7.72 (d, 1H), 8.00 (d, 1H), 9.72 (brs, 1H).	556.4
40		2,5-diCl	2.72 (m, 2H), 2.86 (s, 6H), 3.19 (m, 1H), 3.30 (dd, 1H), 3.98 (m, 2H), 4.07 (m, 2H), 4.29 (m, 1H), 5.60 (d, 1H), 6.86 (d, 2H), 7.55 (m, 3H), 7.66 (s, 1H), 7.70 (d, 1H), 7.95 (d, 1H), 8.72 (brs, 1H).	544.4
41		2,5-diCl	1.87 (m, 2H), 2.31 (m, 2H), 2.87 (s, 6H), 3.21 (m, 1H), 3.31 (dd, 1H), 3.96 (m, 2H), 4.07 (m, 2H), 4.32 (m, 1H), 5.94 (brs, 1H), 6.88 (d, 2H), 7.39 (d, 2H), 7.60 (d, 1H), 7.71 (m, 2H), 8.00 (d, 1H), 9.80 (brs, 1H).	558.4

42		2,5-diCl	2.85 (s, 6H), 3.17 (m, 1H), 3.29 (dd, 1H), 3.95 (m, 2H), 4.29 (m, 1H), 4.62 (d, 2H), 5.86 (d, 1H), 6.35 (m, 1H), 6.59 (d, 1H), 6.80 (d, 2H), 7.30 (m, 5H), 7.45 (d, 2H), 7.51 (dd, 1H), 7.60 (s, 1H), 7.65 (d, 1H), 7.98 (d, 1H), 9.08 (brs, 1H).	564.4
43		2,5-diCl	0.86 (t, 3H), 1.28 (m, 6H), 1.60 (m, 2H), 2.85 (s, 6H), 3.19 (m, 1H), 3.30 (dd, 1H), 3.83 (m, 2H), 3.98 (m, 2H), 4.32 (m, 1H), 5.98 (brs, 1H), 6.87 (d, 2H), 7.37 (d, 2H), 7.58 (dd, 1H), 7.60 (s, 1H), 7.69 (d, 1H), 7.99 (d, 1H), 10.12 (brs, 1H).	532.5
44		2,5-diCl	2.80 (s, 6H), 3.10 (m, 1H), 3.20 (dd, 1H), 3.31 (t, 2H), 3.94 (m, 2H), 4.00 (m, 2H), 4.27 (m, 1H), 5.62 (d, 1H), 6.82 (d, 2H), 7.20 (m, 1H), 7.30 (m, 4H), 7.50 (d, 2H), 7.52 (dd, 1H), 7.62 (s, 1H), 7.67 (d, 1H), 7.94 (d, 1H), 8.59 (s, 1H).	584.4
45		2,5-diCl	2.88 (s, 6H), 3.20 (m, 1H), 3.30 (dd, 1H), 3.99 (m, 2H), 4.33 (m, 1H), 5.31 (s, 2H), 5.95 (d, 1H), 6.86 (d, 2H), 7.38 (d, 2H), 7.51 (m, 3H), 7.66 (m, 3H), 7.78 (d, 1H), 8.05 (d, 1H), 9.79 (brs, 1H).	563.4
46		2,5-diCl	2.99 (s, 6H), 3.32 (m, 1H), 3.45 (dd, 1H), 4.10 (m, 2H), 4.47 (m, 2H), 4.54 (m, 1H), 5.87 (d, 1H), 6.98 (d, 2H), 7.22 (brs, 2H), 7.60 (d, 2H), 7.67 (dd, 1H), 7.79 (d, 1H), 7.90 (s, 1H), 8.09 (d, 1H), 9.04 (brs, 1H).	505.5

Preparation of Starting Materials for Examples 12-46

The appropriate 2-chloro-4-(*N*-alkylated)anilinopyrimidine intermediates of Formula (S1-1) for Examples 12-17 and 19-46 above are either commercially available or are readily prepared by standard methods from known materials, according to Scheme 2. For example,

5 the following reactions (Methods A and E) are illustrations, but not limitations, of the preparation of some of the starting materials used in the above Examples.

**Scheme 2****Reference Example A-3**10 **2-Chloro-4-(2-bromo-4-methylanilino)pyrimidine**

2,4-Dichloropyrimidine (1 g, 6.71 mmol), 2-bromo-4-methylaniline (1.25 g, 6.71 mmol) and di-isopropylethylamine (1.29 ml, 7.38 mmol) were dissolved in *n*-butanol (5 ml). The reaction mixture was heated at 120°C for 12 hours, cooled and evaporated onto silica (5 ml). The residue was purified by column chromatography and eluted with EtOAc

15 (30%):isohexane to give the title product as a solid on evaporation (1.01 g). NMR (300 MHz):

2.31 (s, 3H), 6.50 (d, 1H), 7.22 (dd, 1H), 7.36 (d, 1H), 7.55 (s, 1H), 8.09 (d, 1H), 9.61 (s, 1H);
m/z: (ES⁺) 298.1 (MH⁺).

Reference Example A-4

5 2-Chloro-4-(2,5-dichloroanilino)pyrimidine

2,4-Dichloropyrimidine (50 g, 0.34 mol), 2,5-dichloroaniline (54.38 g, 0.34 mol) and concentrated hydrochloric acid (cat. amount) were dissolved in *n*-butanol (250 ml). The reaction mixture was stirred at room temperature for 12 hours after which the solid that had formed was collected by filtration. The organics were allowed to stand for 48 hours and the
10 solid that formed was collected by filtration, washed with EtOAc and dried to give the title product as a white solid (18.65 g). NMR (300 MHz): 6.82 (d, 1H), 7.31 (dd, 1H), 7.58 (d, 1H), 7.82 (s, 1H), 8.19 (d, 1H), 9.82 (s, 1H); m/z: (ES⁺) 273.9 (MH⁺).

Method E: N-alkylation of 2-chloro-4-anilinopyrimidines.

15 A suitable alkylating agent (commercially available) is of the formula R₁-X where X is a leaving group, such as chloro or bromo.

Reference Example E-1

2-Chloro-4-(N-cyanomethyl-2-bromo-4-methylanilino)pyrimidine

20 2-Chloro-4-(2-bromo-4-methylanilino)pyrimidine (500 mg, 1.68 mmol), chloroacetonitrile (0.13 ml, 2.02 mmol) and potassium carbonate (279 mg, 2.02 mmol) were dissolved in DMF (3 ml). The reaction mixture was stirred at room temperature for 12 hours. Chloroacetonitrile (0.13 ml, 2.02 mmol) and potassium carbonate (279 mg, 2.02 mmol) were again added, and the reaction mixture was stirred at room temperature for a further 48 hours.
25 The reaction mixture was evaporated onto silica (5 ml) and purified by column chromatography eluting with EtOAc (0-40%):isohexane to give the title product as a solid on evaporation (537 mg). NMR (300 MHz): 2.38 (s, 3H), 4.82 (d, 1H), 4.99 (d, 1H), 6.09 (brs, 1H), 7.41 (m, 2H), 7.71 (s, 1H), 8.16 (brd, 1H); M.S. (ES⁺) 337.2 (MH⁺).

30 For Example 18, 2-chloro-4-[indan-5-yl(*N*-cyanomethyl)amino]pyrimidine was prepared by reaction of 2,4-dichloropyrimidine with 5-aminoindane by analogy with Method

A above, followed by *N*-alkylation using chloroacetonitrile (by analogy with Reference Example E-1 above).

Example 47

5 **2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(2-ethylanilino)pyrimidine**

2-Chloro-4-(2-ethylanilino)pyrimidine (Reference Example A-5; 210 mg, 0.90 mmol) was dissolved in *n*-butanol (20 ml). To this solution was added a hot solution of 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline hydrochloride (Reference Example D-1; 229 mg, 0.81 mmol) in methanol (2 ml). The reaction mixture was heated at 100°C for 18 hours, allowed to cool to ambient temperature and then evaporated onto silica (3 ml). The residue was purified by column chromatography eluting with 0-5% 2.0M methanolic ammonia solution in DCM to give the title product as a colourless solid (201 mg, 61%). NMR (300 MHz): 1.09 (t, 3H), 2.17 (s, 6H), 2.31 (m, 2H), 2.58 (q, 2H), 3.80 (m, 3H), 5.96 (d, 1H), 6.72 (d, 2H), 7.20 (m, 3H), 7.36 (d, 1H), 7.53 (d, 2H), 7.89 (d, 1H), 8.56 (s, 1H), 8.76 (s, 1H); m/z: (ES⁺) 408.3 (MH⁺)

10
15

Examples 48-66 :

Examples 48-66 of Formula (S1-2) wherein R₁ is hydrogen, were prepared by the method of Example 47 according to Scheme 1, using 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline (Reference Example D-1) and the appropriate 2-chloro-4-anilinopyrimidine of Formula (S1-1) wherein R₁ is hydrogen. The appropriate 2-chloro-4-anilinopyrimidine starting materials of Formula (S1-1) wherein R₁ is hydrogen are either commercially available or are readily prepared by standard methods from known materials (by analogy to Method A and the corresponding Reference Examples A-1 - A-10).

20
25

Ex No	R ₂	NMR (300 MHz)	m/z (MH ⁺)
48	2-(CH ₂) ₅ CH ₃	0.77 (t, 3H), 1.18(m, 6H) 1.44 (m, 2H), 2.18 (s, 6H), 2.30 (m, 2H), 3.80 (m, 3H), 5.98 (d, 1H), 6.69 (d, 2H), 7.20 (m, 3H), 7.37 (d, 1H), 7.50 (d, 2H), 7.87 (d, 1H), 8.57 (s, 1H), 8.76 (s, 1H).	464.4
49	2-Cl	2.19 (s, 6H), 2.31 (m, 2H), 3.75 (m, 1H), 3.83 (m, 2H), 6.21 (d, 1H), 6.72 (d, 2H), 7.18 (m, 1H), 7.33 (m, 1H), 7.50 (m, 2H), 7.82 (m, 1H), 7.96 (m, 1H), 8.78 (s, 1H), 8.86 (s, 1H).	414.3
50	2-morpholino	2.18 (s, 6H), 2.31 (m, 2H), 2.81 (m, 4H), 3.72 (m, 4H), 3.78 (m, 1H), 3.88 (m, 2H), 4.85 (br, 1H), 6.31 (d, 1H), 6.80 (d, 2H), 7.1 (m, 3H), 7.58 (d, 2H), 7.98 (d, 2H), 8.24 (s, 1H), 8.88 (s, 1H).	465.5
51	2-CO ₂ Me	2.19 (s, 6H), 2.31 (m, 2H), 3.82 (m, 6H), 4.75 (br, 1H), 6.28 (d, 1H), 6.82 (d, 2H), 7.10 (t, 1H), 7.56 (d, 2H), 7.96 (d, 1H), 8.04 (d, 1H), 8.54 (d, 1H), 9.04 (s, 1H).	438.3
52	2-SMe	2.17 (s, 6H), 2.31 (m, 2H), 2.39 (s, 3H), 3.80 (m, 3H), 4.72 (br, 1H), 6.02 (d, 1H), 6.70 (d, 2H), 7.22 (m, 2H), 7.37 (m, 1H), 7.49 (m, 3H) 7.92 (d, 1H), 8.58 (s, 1H), 8.79 (s, 1H).	426.3
53	4-NMe ₂	2.18 (s, 6H), 2.32 (m, 2H), 2.84 (s, 6H), 3.83 (m, 3H), 4.75 (br, 1H), 6.01 (d, 1H), 6.70 (d, 2H), 6.80 (d, 2H), 7.40 (d, 2H), 7.59 (d, 2H) 7.86 (d, 1H), 8.77 (s, 1H), 8.87 (s, 1H).	423.3
54	2-(CH ₂) ₂ CH ₃	0.82 (t, 3H), 1.49 (sextuplet, 2H), 2.18 (s, 6H), 2.32 (m, 2H), 2.58 (t, 2H), 3.80 (m, 3H), 4.74 (br, 1H), 5.98 (d, 1H), 6.68 (d, 2H), 7.20 (m, 3H), 7.38 (d, 1H), 7.51 (d, 2H) 7.88 (d, 1H), 8.57 (s, 1H), 8.77 (s, 1H).	422.3

55	4-Br	2.18 (s, 6H), 2.33 (m, 2H), 3.83 (m, 3H), 4.76 (br, 1H), 6.17 (d, 1H), 6.83 (d, 2H), 7.41 (d, 2H), 7.52 (d, 2H), 7.68 (d, 2H) 7.98 (d, 1H), 8.96 (s, 1H), 9.40 (s, 1H).	460.4
56	2-F-5-Me	2.18 (s, 6H), 2.31 (m, 5H), 3.81 (m, 3H), 4.74 (br, 1H), 6.22 (d, 1H), 6.78 (d, 2H), 6.90 (m, 1H), 7.12 (m, 1H), 7.51 (d, 2H) 7.77 (d, 1H), 7.98 (d, 1H), 8.88 (s, 1H).	412.4
57	2-I	2.18 (s, 6H), 2.31 (m, 2H), 3.80 (m, 3H), 4.74 (br, 1H), 6.04 (d, 1H), 6.67 (d, 2H), 7.00 (m, 1H), 7.47 (m, 4H), 7.95 (m, 2H), 8.72 (s, 1H), 8.82 (s, 1H).	506.4
58	2-F-4-Me	2.19 (s, 6H), 2.31 (m, 5H), 3.83 (m, 3H), 4.76 (br, 1H), 6.19 (d, 1H), 6.77 (d, 2H), 6.98 (d, 1H), 7.09 (d, 1H), 7.52 (d, 2H) 7.78 (t, 1H), 7.96 (d, 1H), 8.83 (s, 1H).	412.4
59	4-F	2.19 (s, 6H), 2.32 (m, 2H), 3.82 (m, 3H), 4.77 (br, 1H), 6.14 (d, 1H), 6.82 (d, 2H), 7.10 (t, 2H), 7.57 (d, 2H), 7.66 (t, 2H) 7.97 (d, 1H), 8.92 (s, 1H), 9.25 (s, 1H).	398.4
60	2-CN	2.18 (s, 6H), 2.31 (m, 2H), 3.81 (m, 3H), 4.74 (br, 1H), 6.22 (d, 1H), 6.71 (d, 2H), 7.32 (t, 1H), 7.44 (d, 2H), 7.76 (m, 3H), 8.02 (d, 1H), 8.96 (s, 1H), 9.41 (s, 1H).	405.4
61	4-COMe	(MeOH- δ_4): 2.36 (s, 6H), 2.54 (m, 5H), 4.00 (m, 3H), 6.20 (d, 1H), 6.96 (d, 2H), 7.43 (d, 2H), 7.81 (d, 2H), 7.89 (d, 2H) 7.95 (d, 1H).	422.4
62	2-Br	2.19 (s, 6H), 2.31 (m, 2H), 3.80 (m, 3H), 4.77 (br, 1H), 6.20 (d, 1H), 6.76 (d, 2H), 7.16 (m, 1H), 7.42 (m, 1H), 7.52 (d, 2H) 7.74 (m, 2H), 7.99 (d, 1H), 8.79 (s, 1H), 8.90 (s, 1H).	458.3
63	2-Cl-5-Me	2.20 (s, 6H), 2.29 (s, 3H), 2.30 (m, 1H), 2.41 (dd, 1H), 3.77 (m, 1H), 3.88 (m, 2H), 4.79 (br, 1H), 6.20 (d, 1H), 6.72 (d, 2H), 6.99 (d, 1H), 7.37 (d, 1H), 7.50 (d, 2H) 7.62 (s, 1H), 7.95 (d, 1H), 8.72 (s, 1H), 8.89 (s, 1H).	428.5

64	2-OEt	1.34 (t, 3H), 2.19 (s, 6H), 2.34 (m, 2H), 3.80 (m, 1H), 3.88 (m, 2H), 4.09 (q, 2H), 4.78 (m, 1H), 6.27 (d, 1H), 6.78 (d, 2H), 6.92 (m, 1H), 7.05 (m, 2H), 7.56 (d, 2H), 7.95 (m, 2H), 8.32 (s, 1H), 8.88 (s, 1H).	424.5
65	2-F-5-CF ₃	2.17 (s, 6H), 2.31 (m, 2H), 3.77 (m, 1H), 3.83 (m, 2H), 4.73 (d, 1H), 6.32 (d, 1H), 6.74 (d, 2H), 7.45 (m, 4H), 8.02 (d, 1H), 8.32 (m, 1H), 8.97 (s, 1H), 9.12 (s, 1H).	466.5
66	2-OMe	2.19 (s, 6H), 2.33 (m, 2H), 3.83 (m, 6H), 4.77 (br, 1H), 6.27 (d, 1H), 6.78 (d, 2H), 6.92 (m, 1H), 7.02 (m, 2H), 7.56 (d, 2H), 7.93 (d, 1H), 8.01 (d, 1H), 8.42 (s, 1H), 8.92 (s, 1H).	410.4

Preparation of Starting Materials for Examples 47-66

The 2-chloro-4-anilinopyrimidine starting materials for Examples 47-66 above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions (Method A of Scheme 2) are illustrations, but not limitations, of the preparation of some of the starting materials used in the above Examples.

Reference Example A-5

10 2-Chloro-4-(2-ethylanilino)pyrimidine

2,4-Dichloropyrimidine (596 mg, 4 mmol), 2-ethylaniline (494 ml, 4 mmol) and *N,N*-diisopropylethylamine (695 ml, 4 mmol) were dissolved in *n*-butanol (20 ml) with stirring. The reaction mixture was heated to 100°C for 18 hours, allowed to cool to ambient temperature and evaporated onto silica (3 ml). The residue was purified by column chromatography eluting with EtOAc (0-20%): isohexane to give the title product as a colourless solid on evaporation (215 mg, 23%). NMR (CDCl₃, 300 MHz): 1.20 (t, 3H), 2.61 (q, 2H), 6.26 (d, 1H), 6.80 (br, 1H) 7.31 (m, 4H), 8.04 (d, 1H); m/z: (ES⁺) 234.2 (MH⁺).

Reference Example A-6**2-Chloro-4-(2-methoxycarbonylanilino)pyrimidine**

2,4-Dichloropyrimidine (596 mg, 4 mmol), methyl 2-aminobenzoate (517 ml, 4 mmol) and 2,6-lutidine (465 ml, 4 mmol) were dissolved in *n*-butanol (20 ml) with stirring. The reaction mixture was heated to 120°C for 24 hours, allowed to cool to ambient temperature and evaporated onto silica (3 ml). The residue was purified by column chromatography eluting with EtOAc (0-20%): isohexane to give the title product as a colourless solid on evaporation (137 mg, 13%). NMR (CDCl₃, 300 MHz): 3.97 (s, 3H), 6.63 (d, 1H), 7.09 (t, 1H) 7.61 (m, 1H), 8.05 (d, 1H), 8.19 (d, 1H), 8.74 (d, 1H); m/z: (ES⁺) 264.3 (MH⁺).

10

Reference Example A-7**2-Chloro-4-(2-cyanoanilino)pyrimidine**

2,4-Dichloropyrimidine (149 mg, 1 mmol), 2-cyanoaniline (118 mg, 1 mmol) and 2 drops conc. HCl were dissolved in water (20 ml). The reaction mixture was stirred at ambient temperature for 18 hours. The resulting precipitate was filtered off and dried under vacuum to give the title product as a colourless solid (84 mg, 36%). NMR (300 MHz) 6.79 (d, 1H), 7.42 (m, 1H), 7.62 (m, 1H), 7.75 (m, 1H), 7.89 (m, 1H), 8.24 (d, 1H), 10.23 (br, 1H); m/z: (ES⁺) 231.1 (MH⁺).

Reference Example A-8**2-Chloro-4-(2-fluoro-5-trifluoromethyl)anilinopyrimidine**

2,4-Dichloropyrimidine (596 mg, 4 mmol), 2-fluoro-5-trifluoromethylaniline (520 µl, 4 mmol) and 2 drops conc. HCl were dissolved in *n*-butanol (20 ml) with stirring. The reaction mixture was stirred at ambient temperature for 18 hours and then evaporated onto silica (3 ml). The residue was purified by column chromatography eluting with EtOAc (5-50%): isohexane to give the title product as a colourless solid on evaporation (93 mg, 8%). NMR (CDCl₃, 300 MHz): 6.60 (d, 1H), 6.99 (br, 1H), 7.27 (m, 1H), 7.42 (m, 1H), 8.25 (d, 1H), 8.41 (m, 1H); m/z: (ES⁺) 292.1 (MH⁺).

30

Example 67**2-Anilino-4-{4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]anilino}pyrimidine**

2-Anilino-4-chloropyrimidine (145 mg, 0.71 mmol) was dissolved in *n*-butanol (20 ml). To this solution was added a hot solution of 4-[3-(*N,N*-dimethyl)amino-2-hydroxy-
5 propoxy]aniline hydrochloride (Reference Example D-1; 178 mg, 0.63 mmol) in methanol (2 ml). The reaction mixture was heated at 80°C for 18 hours, allowed to cool to ambient temperature and then evaporated onto silica (3 ml). The residue was purified by column chromatography eluting with 0-8% 2.0M methanolic ammonia solution in DCM to give the
10 title product as a colourless solid (157 mg, 65%). NMR (300 MHz): 2.18 (s, 6H), 2.33 (m, 2H), 3.83 (m, 3H), 4.77 (d, 1H), 6.11 (d, 1H), 6.86 (m, 3H), 7.19 (m, 2H), 7.51 (d, 2H), 7.69 (d, 2H), 7.96 (d, 1H), 9.01 (s, 1H), 9.08 (s, 1H); m/z: (ES⁺) 380.4 (MH⁺).

Method F: Conversion of 2-anilino-4-hydroxypyrimidines to 2-anilino-4-chloropyrimidines.**Reference Example F-1****15 2-Anilino-4-chloropyrimidine**

2-Anilino-4-hydroxypyrimidine (Reference Example G-1) (750 mg, 4.01 mmol) was dissolved in phosphorus oxychloride (5 ml). To this solution was added phosphorus pentachloride (918 mg, 4.41 mmol) and the reaction mixture heated to 110°C for 18 hours. The reaction mixture was then allowed to cool to ambient temperature and slowly added to
20 cool (20-30°C) water (25 ml) with vigorous stirring. This was then left to stir for 60 mins before being extracted with EtOAc (2 x 15 ml). The organic layers were combined and washed with NaHCO₃ (aq) (2 x 10 ml), brine (10 ml) and then evaporated onto silica (3 ml). The residue was purified by column chromatography eluting with 0-20% EtOAc in isohexane to give the title product as a colourless solid (492 mg, 60%). NMR (CDCl₃, 300 MHz): 6.78
25 (m, 1H), 7.09 (m, 1H), 7.19 (br, 1H), 7.36 (m, 2H), 7.59 (d, 2H), 8.28 (d, 1H); m/z: (ES⁺) 206.0 (MH⁺).

Method G: Reaction of 2-methylthio-4-hydroxypyrimidine with an aniline**Reference Example G-1****2-Anilino-4-hydroxypyrimidine**

2-Methylthio-4-hydroxypyrimidine (1.42 g, 10 mmol) was dissolved in 2-methoxyethylether (10 ml). To this solution was added aniline (910 μ l, 10 mmol) and the reaction mixture heated at 160°C for 18 hours. The resulting precipitate was filtered off and washed with diethyl ether (10 ml), water (10 ml), diethyl ether (2 x 10 ml) and dried under vacuum to give the title product as a colourless solid (1.296 g, 69%). NMR (300 MHz): 5.79, (d, 1H), 6.99 (t, 1H), 7.24 (m, 2H), 7.57 (m, 2H), 7.73 (m, 1H), 8.80 (br, 1H); m/z: (ES⁺) 188.1 (MH⁺).



Examples 68-73

Examples 68-73 of Formula (S1-2) were prepared by the method of Example 2 according to Scheme 1, using 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline (Reference Example D-1) and the appropriate 2-chloro-4-anilinopyrimidine intermediate of Formula (S1-1), 2-chloro-4-[indan-5-ylamino]pyrimidine (for Example 70) and 2-chloro-4-(*N*-methyl)anilinopyrimidine (for Example 73).

The appropriate 2-chloro-4-anilinopyrimidine starting materials of Formula (S1-1) are either commercially available or are readily prepared by standard methods from known materials (by analogy to Method A and the corresponding Reference Examples A-1 - A-10).

For Example 70, 2-chloro-4-[indan-5-ylamino]pyrimidine was prepared by reaction of 2,4-dichloropyrimidine with 5-aminoindane (by analogy to Method A and the corresponding Reference Examples A-1 - A-10).

For Example 73, 2-chloro-4-(*N*-methyl)anilinopyrimidine was prepared from 2,4-dichloropyrimidine and *N*-methylaniline (by analogy to Method A and the corresponding Reference Examples A-1 - A-10).

Ex No	R ₁	R ₂	NMR (300 MHz)	m/z (MH ⁺)
68	H	4-cyclohexyl	1.3 (m, 6H), 1.8 (m, 5H), 2.6 (s, 6H), 2.9 (m, 2H), 3.9 (d, 2H), 4.1 (m, 1H), 6.1 (d, 1H) 6.8 (d, 2H), 7.1 (d, 2H), 7.6 (m, 4H), 7.9 (d, 1H), 8.9 (s, 1H), 9.2 (s, 1H).	462
69	H	2-phenyl	2.8 (s, 6H), 3.2 (m, 4H), 3.9 (m, 1H), 5.9 (d, 1H), 6.0 (d, 1H), 6.7 (d, 2H), 7.3-7.5 (m, 12H), 7.8 (d, 1H)	456
70	H	 So that Q2 is 	2.0 (m, 2H), 3.8 (s, 6H), 3.8 (m, 4H), 3.1 (m, 2H), 3.9 (d, 2H), 4.2 (m, 1H), 6.1 (d, 1H), 6.8 (d, 2H), 7.1 (d, 1H), 7.3 (d, 1H), 7.6 (m, 3H), 7.9 (d, 1H), 8.9 (s, 1H), 9.1 (s, 1H).	420
71	H	3-SO ₂ CH ₂ -CH ₂ OH	2.9 (s, 6H), 3.2 (m, 1H), 3.3 (m, 1H), 3.4 (m, 2H), 3.7 (m, 2H), 4.0 (m, 2H), 4.3 (m, 1H), 6.4 (d, 1H), 6.9 (d, 2H), 7.5 (m, 4H), 8.0 (q, 2H), 8.1 (m, 1H).	488
72	H	2-S-F ₃ Ph	2.2 (s, 6H), 3.7 (m, 1H), 3.8 (m, 3H), 4.7 (m, 1H), 6.0 (d, 1H), 6.6 (d, 2H), 7.2 (m, 1H), 7.4 (m, 5H), 7.9 (d, 1H), 8.8 (s, 1H), 9.0 (s, 1H).	578
73	Me	H	2.2 (s, 6H), 2.3 (m, 2H), 3.4 (s, 3H), 3.8 (m, 3H), 4.7 (d, 1H), 5.7 (d, 1H), 6.8 (d, 2H), 7.3 (m, 3H), 7.4 (m, 2H), 7.6 (d, 2H), 7.8 (d, 1H), 8.9 (s, 1H).	394

Examples 74-77

Examples 74-77 of Formula (S1-2) wherein R₁ is hydrogen, were prepared by using a robot by the method of Example 2 according to Scheme 1, using 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline (Reference Example D-1) and the appropriate 2-chloro-4-anilinopyrimidine of Formula (S1-1) wherein R₁ is hydrogen. The appropriate 2-chloro-4-anilinopyrimidine starting materials of Formula (S1-1) wherein R₁ is hydrogen are either

commercially available or are readily prepared by standard methods from known materials (by analogy to Method A and the corresponding Reference Examples A-1 - A-10).

The following conditions were used:

- (i) evaporations were carried out *in vacuo* using a Savant AES 2000;
- 5 (ii) operations were carried out using a Zymate XP robot with solution additions via a Zymate Master Laboratory Station and stirred in a Stem RS5000 Reacto-Station at 25°C;
- (iii) column chromatography was performed using either an Anachem Sympur MPLC or Jones Flashmaster MPLC systems on Silica using a Mega Bond Elut column (10 g);
- (iv) the structures of the end products was confirmed by L.C.M.S. on a Micromass

10 OpenLynx system using the following:

Column: 4.6 mm x 10 cm Hichrom RPB 5Å

Solvent: A = 95% Water + 0.1% Formic acid, B = 95% Acetonitrile + 0.1%
Formic acid

Run time: 15 minutes with a 10 minute gradient from 5 - 95% B

15 Wavelength: 254nm, bandwidth 10nm

Mass detector Platform LC

Ex No	R ₂	m/z [MH ⁺]	HPLC retention time (min)
74	3-acetamido	437	2.20
75	2-benzimidazol-2-yl	496	6.69
76	4-(2-chloro-1,1,2-trifluoroethoxy)-	512	7.41
77	4-phenoxy	472	7.47

Examples 78-85



20 Examples 78-85 of Formula (S1-2) were prepared by the method of Example 2, according to Scheme 1, using 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline (Reference Example D-1) and the appropriate 2-chloro-4-(*N*-alkylated)anilinopyrimidine intermediate of Formula (S1-1) or, for Example 84, 2-chloro-4-[indan-5-yl(*N*-3-phenylprop-2-enyl)amino]pyrimidine.

25 The appropriate 2-chloro-4-(*N*-alkylated)anilinopyrimidine intermediates of Formula (S1-1) were prepared according to Scheme 2 by analogy to Method E described above and

further below, using the appropriate 2-chloro-4-anilinopyrimidine intermediate (prepared by analogy to Method A and the corresponding Reference Examples A-1 - A-10) and the appropriate alkylating agent.

For Example 84, 2-chloro-4-[indan-5-yl(*N*-3-phenylprop-2-enyl)amino]pyrimidine
 5 was prepared by reaction of 2,4-dichloropyrimidine with 5-aminoindane (by analogy to Method A and the corresponding Reference Examples A-1 - A-10), followed by reaction with 3-phenylprop-2-enylchloride or bromide by analogy with Method E.

Ex No	R ₁	R ₂	NMR (400 MHz, 373K)	m/z (MH ⁺)
78	-CH ₂ CH ₂ CH ₂ CF ₃	2-F-5-CH ₃	1.97 (m, 2H), 2.38 (m, 2H), 2.47 (s, 3H), 2.99 (s, 6H), 3.33 (m, 1H), 3.44 (dd, 1H), 4.09 (m, 4H), 4.43 (m, 1H), 5.98 (d, 1H), 7.02 (d, 2H), 7.41 (m, 3H), 7.57 (d, 2H), 8.06 (d, 1H), 9.73 (bs, 1H).	522.6
79	-CH ₂ CH ₂ CH ₂ CF ₃	3,4-diCl	1.82 (m, 2H), 2.29 (m, 2H), 2.85 (s, 6H), 3.19 (m, 1H), 3.30 (dd, 1H), 3.96 (m, 4H), 4.32 (m, 1H), 5.98 (d, 1H), 6.88 (d, 2H), 7.37 (dd, 1H), 7.42 (d, 2H), 7.67 (s, 1H), 7.73 (d, 1H), 7.94 (d, 1H), 9.56 (bs, 1H).	558.6
80	-CH ₂ CH=CHBr	2-F-5-CH ₃	2.25 (s, 6H), 2.34 (s, 3H), 2.37 (m, 1H), 2.46 (dd, 1H), 3.90 (m, 3H), 4.44 (d, 1H), 4.60 (d, 1H), 5.70 (d, 1H), 6.45 (bm, 2H), 6.80 (m, 2H), 7.51 (m, 2H), 7.92 (m, 1H), 8.57 (s, 1H).	530.4

81	-CH ₂ CH=CHPh	2-F-4-CH ₃	2.27 (s, 6H), 2.43 (m, 5H), 3.92 (m, 3H), 4.32 (bs, 1H), 4.66 (d, 2H), 5.77 (d, 1H), 6.39 (m, 1H), 6.59 (d, 1H), 6.81 (d, 2H), 7.19 (m, 2H), 7.27 (m, 1H), 7.35 (m, 5H), 7.54 (d, 2H), 7.95 (d, 1H), 8.56 (s, 1H).	528.5
82	-CH ₂ CH=CHPh	2-F-5-CH ₃	2.23 (s, 6H), 2.32 (s, 3H), 2.39 (m, 2H), 3.88 (m, 3H), 4.30 (bs, 1H), 4.63 (d, 2H), 5.77 (d, 1H), 6.32 (m, 1H), 6.59 (d, 1H), 6.78 (d, 2H), 7.27 (m, 8H), 7.50 (d, 2H), 7.91 (d, 1H), 8.51 (s, 1H).	528.5
83	-CH ₂ CH=CHPh	2-CN	2.23 (s, 6H), 2.33 (m, 1H), 2.44 (dd, 1H), 3.88 (m, 3H), 4.29 (bs, 1H), 4.70 (d, 2H), 5.83 (d, 1H), 6.37 (m, 1H), 6.60 (d, 1H), 6.75 (d, 2H), 7.21 (d, 1H), 7.31 (m, 4H), 7.44 (d, 2H), 7.58 (d, 2H), 7.82 (m, 1H), 7.91 (d, 1H), 7.99 (d, 1H), 8.59 (s, 1H).	521.5
84	-CH ₂ CH=CHPh	 So that Q2 is 	2.09 (m, 2H), 2.22 (s, 6H), 2.34 (m, 1H), 2.42 (dd, 1H), 2.93 (m, 4H), 3.89 (m, 3H), 4.28 (bs, 1H), 4.67 (d, 2H), 5.71 (d, 1H), 6.38 (m, 1H), 6.55 (d, 1H), 6.80 (d, 2H), 7.08 (d, 1H), 7.20 (m, 2H), 7.32 (m, 5H), 7.56 (d, 2H), 7.83 (d, 1H), 8.43 (s, 1H).	536.6

85	-(CH ₂) ₆ OH	2,5-diCl	1.35 (m, 4H), 1.44 (m, 2H), 1.63 (m, 2H), 2.86 (s, 6H), 3.20 (m, 1H), 3.32 (dd, 1H), 3.41 (t, 2H), 3.81 (t, 2H), 3.97 (m, 2H), 4.31 (m, 1H), 5.76 (d, 1H), 6.83 (d, 2H), 7.47 (d, 2H), 7.52 (m, 2H), 7.68 (d, 1H), 7.96 (d, 1H), 8.89 (bs, 1H).	548.5
----	-------------------------------------	----------	---	-------

Preparation of Starting Materials for Examples 78-85

The appropriate 2-chloro-4-(*N*-alkylated)anilinopyrimidine intermediates of Formula (S1-1) for Examples 78-83 and 85 above are either commercially available or are readily prepared by standard methods from known materials, according to Scheme 2. For example, the following reactions are further illustrations, but not limitations, of the preparation of some of the starting materials used in the above Examples.

Reference Example E-2

10 2-Chloro-4-[*N*-(4,4,4-trifluorobutyl)-2-fluoro-5-methylanilino]pyrimidine

4-(2-Fluoro-5-methylanilino)-2-chloropyrimidine (Reference Example A-10, 750 mg, 3.16 mmol), 4,4,4-trifluoro-1-bromobutane (725 mg, 3.80 mmol) and potassium carbonate (525 mg, 3.80 mmol) were dissolved in DMF (3 ml). The reaction mixture was stirred at room temperature for 12 hours and then evaporated onto silica (5 ml) and purified by column chromatography eluting with EtOAc (0-40%):isohexane to give the title product as a solid on evaporation (976 mg). NMR (300 MHz, 373K): 1.79 (m, 2H), 2.28 (m, 2H), 2.33 (s, 3H), 3.91 (t, 2H), 6.19 (d, 1H), 7.28 (m, 3H), 8.03 (d, 1H); *m/z* (EI⁺) 347 (M⁺).

The Table immediately below shows by analogy to a Reference Example how the various intermediates for Examples 78-85 were prepared. The appropriate Intermediate A (un-*N*-alkylated 2-chloropyrimidine) being prepared by the relevant Method A and the appropriate Intermediate E (*N*-alkylated 2-chloropyrimidine) being prepared by the relevant Method E.

Methods used	Ex No	Intermediate A m/z (MH ⁺)	Intermediate E m/z (MH ⁺)
A-3 + E-2	78	238.1	348
A-3 + E-2	79	274.1	384
A-3 + E-2	80	238.1	356
A-3 + E-2	81	238.1	354.3
A-3 + E-2	82	238.1	354.3
A-7 + E-2	83	231.1	347.2
A-3 + E-2	84	246.2	362.3
A-4 + E-1	85	273.9	374.2

Example 86

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(*N*-(2-phenylethyl)anilino)pyrimidine

- 5 2-Chloro-4-(*N*-(2-phenylethyl)anilino)pyrimidine (Reference Example E-3; 270 mg, 0.87 mmol) was dissolved in NMP (2 ml), 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]aniline hydrochloride (Reference Example D-1; 222 mg, 0.90 mmol) was added and the mixture heated at 120°C for 12 hours. The solvent was evaporated, the residue was resolubilized in methanol/ammonia 6M and evaporated again to dryness. The resulting solid
- 10 was purified by flash chromatography using increasingly polar solvent mixtures starting with DCM and ending with DCM/methanol with 10% ammonia (87.5/12.5). Evaporation of the solvent gave a foam which was triturated in ether to give the title product as a white solid (150 mg, 36%). NMR: (400 MHz, 353K) 2.30 (s, 6H), 2.50 (m, 2H), 2.90 (m, 2H), 3.80 (m, 1H), 3.85 (m, 1H), 3.95 (br s, 1H), 4.10 (m, 2H), 5.00 (br s, 1H), 5.50 (d, 1H), 6.70 (d, 2H), 7.15
- 15 (m, 3H), 7.25(m, 4H), 7.35 (t, 1H), 7.50 (t, 2H), 7.60 (d, 2H), 7.80 (d, 1H), 8.85 (s, 1H), M.S.: (ES⁺) 484 (MH⁺).

Reference Example E-3

2-Chloro-4-(*N*-(2-phenylethyl)anilino)pyrimidine

- 20 2-Chloro-4-anilinopyrimidine (Reference Example A-9, 600 mg, 2.9 mmol) was dissolved in anhydrous DMF (8 ml) and sodium hydride (140 mg, 3.5 mmol, 60% in oil) was

- 77 -

added portion wise. 10 min later phenethylbromide (478 μ l, 3.5 mmol) was added and the mixture was stirred at ambient temperature for 5 hours. More sodium hydride (140 mg, 3.5 mmol, 60% in oil) and phenethylbromide (478 μ l, 3.5 mmol) were added and stirring was maintained overnight. The solvent was evaporated off and the residue partitioned between water and DCM. The organic phase was dried (MgSO_4) the solvent evaporated. The crude product was purified by flash chromatography using first DCM then EtOAc/ petroleum ether (25/75). The solvent was evaporated to give the title product as a white solid (530 mg, 59 %). NMR (400 MHz, 353K): 2.90 (t, 2H), 4.10 (t, 2H), 6.15 (d, 1H), 7.25 (m, 7H), 7.45 (t, 1H), 7.65 (t, 2H), 8.00 (d, 1H); m/z: (ES^+) 310 and 312 (MH^+).

10

Example 87

2-{4-[3-(*N,N*-Dimethylamino)-2-hydroxypropoxy]anilino}-4-(*N*-(pyrid-4-ylmethyl)anilino)pyrimidine

Using a procedure analogous to that described for Example 86, 2-chloro-4-(*N*-(pyrid-4-ylmethyl)anilino)pyrimidine (Reference Example E-4, 230 mg, 0.77 mmol) gave the title product as a greyish solid (124 mg, 34 %). NMR (400 MHz, 353K): 2.25 (s, 6H), 2.40 (br m, 2H), 3.80 (m, 1H), 3.90 (m, 2H), 4.90 (br s, 1H), 5.25 (s, 2H), 5.80 (d, 1H), 6.70 (d, 1H), 7.30-7.50 (m, 10H), 7.90 (d, 1H), 8.50 (d, 2H), 9.00 (s, 1H); m/z: (ES^+) 471 (MH^+).

20 **Reference Example E-4**

2-Chloro-4-(*N*-(pyrid-4-ylmethyl)anilino)pyrimidine

Using a procedure similar to the one described for Reference Example E-3, 2-chloro-4-anilinopyrimidine (Reference Example A-9, 500 mg, 2.4 mmol) was reacted with 4-bromomethyl pyridine (7.38 mg, 1.2 mmol) to give, after work-up and purification, the title product (230 mg, 32%). NMR (400 MHz, 353K): 5.20 (s, 2H), 6.35 (d, 1H), 7.30 (d, 2H), 7.40 (m, 3H), 7.50 (t, 2H), 8.10 (d, 1H), 8.50 (d, 2H); m/z (ES^+) 297 (MH^+).

30

Example 88**2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(*N*-(2-cyclohexylethyl)anilino)pyrimidine**

Using a procedure similar to the one described for Example 86, 2-chloro-4-(*N*-(2-cyclohexylethyl)anilino)pyrimidine (Reference Example E-5, 360 mg, 1.1 mmol) gave the title product as a greyish solid (211 mg, 40 %). NMR (400 MHz, 353K): 0.90 (m, 2H), 1.20 (m, 3H), 1.30 (m, 1H), 1.50 (m, 2H), 1.65 (m, 5H), 2.65 (s, 3H), 3.00 (m, 2H), 3.90 (m, 4H), 4.15 (br s, 1H), 5.60 (d, 1H), 6.80 (d, 1H), 7.30 (d, 1H), 7.40 (t, 1H), 7.50 (t, 1H), 7.65 (d, 1H), 7.80 (d, 1H), 9.85 (s, 1H); *m/z* (ES⁺) 490 (MH⁺).

10

Reference Example E-5**2-Chloro-4-(*N*-(2-cyclohexylethyl)anilino)pyrimidine**

2-Chloro-4-anilinopyrimidine (Reference Example A-9, 700 mg, 3.4 mmol) was dissolved in DCM (70 ml), triphenyl phosphine (1.07 g, 4.1 mmol) and 2-cyclohexyl ethanol (0.57 ml, 4.1 mmol) were added followed by dropwise addition of DEAD (0.646 ml, 4.1 mmol). After 1 hour additional triphenyl phosphine (0.5 g, 2 mmol), 2-cyclohexyl ethanol (0.28 ml, 2 mmol) and DEAD (0.320 ml, 2 mmol) were added and the reaction mixture was stirred overnight at ambient temperature. The solvent was evaporated off and the residue was purified by flash chromatography using EtOAc/petroleum ether (15/85, then 20/80) as the eluent. The solvent was evaporated to give the title product as a colourless oil (368 mg, 37 %). NMR (400 MHz, 353K): 0.90 (m, 2H), 1.20 (m, 3H), 1.30 (m, 1H), 1.65 (m, 7H), 3.90 (t, 2H), 4.05 (m, 1H), 6.10 (d, 1H), 7.34 (d, 2H), 7.43 (t, 1H), 7.54 (t, 2H), 7.95 (d, 1H); *m/z* (ES⁺) 316 and 318 (MH⁺).

25 **Example 89****2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(*N*-(3-morpholinopropyl)anilino)pyrimidine**

Using a procedure analogous to that described for Example 86 except that heating was at 100°C for 7 hours, 2-chloro-4-(*N*-(3-morpholinopropyl)anilino)pyrimidine (Reference Example E-6, 280 mg, 0.84 mmol) gave the title product as a solid (38 mg, 7 %). NMR (400 MHz, 353K): 2.00 (m, 2H), 2.80 (d, 3H), 2.85 (d, 3H), 3.0 (m, 4H), 3.30 (m, 4H), 3.7 (t, 2H),

30

4.0 (m, 6H), 4.30 (m, 1H), 5.7 (m, 1H), 7.10 (m, 3H), 7.3-7.6 (m, 6H), 7.85 (m, 1H); m/z: (ES⁺) 507 (MH⁺).

Reference Example E-6

5 2-Chloro-4-(N-(3-morpholinopropyl)anilino)pyrimidine

2-Chloro-4-anilinopyrimidine (Reference Example A-9, 400 mg, 1.9 mmol) was dissolved in DCM (23 ml), triphenyl phosphine (612 mg, 2.3 mmol) and 3-N-morpholinopropanol (303 mg, 2.1 mmol) were added followed by dropwise addition of DTAD (537 mg, 2.3 mmol). The reaction mixture was stirred overnight at ambient
10 temperature. The solvent was evaporated off and the residue was purified by flash chromatography using first DCM then EtOAc as the eluent. The solvent was evaporated to give the title product as a colourless oil (560 mg, 88 %). NMR (400 MHz, 353K): 1.70 (m, 2H), 2.30 (m, 6H), 3.55 (m, 4H), 3.90 (m, 2H), 6.15 (m, 1H), 7.35-7.70 (m, 5H), 7.95 (m, 1H); m/z (ES⁺) 333 and 335 (MH⁺).

15

Example 90

2-{4-[3-(N,N-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-(N-(3-phenylprop-2-ynyl)anilino)pyrimidine

Using a procedure analogous to the one described for Example 86 except that heating
20 was at 120°C for 2 hours, 2-chloro-4-(N-(3-phenylprop-2-ynyl)anilino)pyrimidine (Reference Example E-7, 440 mg, 1.3 mmol) gave the title product as a solid (250 mg, 39 %). NMR (400 MHz, 353K): 2.20 (s, 6H), 2.25-2.40 (m, 2H), 3.80 (m, 1H), 3.90 (m, 2H), 4.80 (s, 1H), 4.95 (s, 2H), 5.75 (d, 1H), 6.80 (d, 2H), 7.35 (s, 5H), 7.45 (m, 3H), 7.55 (t, 2H), 7.70 (d, 2H), 7.90 (d, 1H), 9.10 (s, 1H); m/z: (ES⁺) (MH⁺).

25

Reference Example E-7

2-Chloro-4-(N-(3-phenylprop-2-ynyl)anilino)pyrimidine

Using a procedure analogous to that described for Reference Example E-6, 2-chloro-4-anilinopyrimidine (Reference Example A-9, 500 mg, 2.4 mmol) gave, after reaction with
30 triphenylphosphine, DTAD and 3-phenyl-2-propyn-1-ol, the title product as a colourless gum

(440 mg, 57 %). NMR (400 MHz, 353K): 4.95 (s, 2H), 6.30 (d, 1H), 7.35 (s, 5H), 7.45 (m, 3H), 7.60 (m, 2H), 8.10 (d, 1H); m/z: (ES⁺) 320 and 322 (MH⁺).

Example 91

5 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxypropoxy]anilino}-4-anilinopyrimidine

4-Anilino-2-(4-(2,3-epoxypropoxy)anilino)pyrimidine (Reference Example I-1, 0.61 g, 1.84 mmol) was dissolved in DMF (2 ml) and treated with dimethylamine (6 mmol, 3 ml of a 2M solution in EtOH). After stirring overnight at ambient temperature the reaction mixture was partitioned between EtOAc and water. The organic phase was washed with water, dried
10 over MgSO₄ and evaporated at reduced pressure. The residue was purified by chromatography (0.1% NH₃ (aq), 3-10% MeOH in DCM as eluent). Upon evaporation of the fractions, an oily product was obtained, this was triturated with ether to give the title product as a white solid (0.126 g, 18%). NMR (300 MHz): 2.2 (s, 6H), 2.3-2.8 (m, 2H), 3.75-3.95 (m, 3H), 4.82 (brs, 1H), 6.17 (d, 1H), 6.82 (d, 2H), 6.97 (t, 1H), 7.27 (t, 2H), 7.58 (d, 2H), 7.66 (d, 2H), 7.95 (d,
15 1H), 8.95 (s, 1H), 9.25 (s, 1H); m/z: (ES⁺) 380.4 (MH⁺).

Reference Example A-9

2-Chloro-4-anilinopyrimidine

2,4-Dichloropyrimidine (3.75 g, 25 mmol) was dissolved in EtOH (12 ml) and treated
20 with aniline (2.27 ml, 25 mmol) and triethylamine (3.82 ml, 27.2 mmol). The reaction mixture was heated to reflux for 6 hours, partitioned between EtOAc and water. The organic phase was washed with 1M HCl, dried over MgSO₄ and evaporated to obtain a cream coloured solid. This material was purified by chromatography (25-50% EtOAc in isohexane) to give the title product as an off white solid. NMR (300 MHz) 6.73 (d, 1H), 7.08 (t, 1H), 7.35 (t,
25 2H), 7.57 (d, 2H), 8.12 (d, 1H), 9.95 (brs, 1H); m/z: (ES⁺) 206 (MH⁺).

Method H: Reaction of 4-anilino-2-chloropyrimidines with anilines.

Reference Example H-1

4-Anilino-2-(4-hydroxyanilino)pyrimidine

30 4-Anilino-2-chloropyrimidine (Reference Example A-9, 0.921 g, 4.48 mmol) was dissolved in butanol (6 ml) and treated with 4-hydroxyaniline (0.489 g, 4.48 mmol) and conc.

HCl (9 drops). The reaction was heated to 80°C for 4 hours. The solvent was removed by evaporation at reduced pressure to give the title product as a solid which was used without further purification (1.4 g) NMR (300 MHz): 6.43 (d, 1H), 6.68 (d, 2H) 7.14 (t, 1H), 7.25 (m, 4H), 7.64 (m, 2H), 7.88 (s, 1H) 9.53 (brs, 1H), 10.27 (brs, 1H), 10.88 (brs, 1H); m/z: (ES⁺) 279 (MH⁺).

Method I: Reaction of 4-anilino-2-(4-hydroxyanilino)pyrimidines with bromoalkylepoxides.

Reference Example I-1

4-Anilino-2-[4-(2,3-epoxypropoxy)anilino]pyrimidine

10 4-Anilino-2-(4-hydroxyanilino)pyrimidine (Reference Example H-1, 0.541 g, 1.95 mmol) was dissolved in DMSO (2 ml) and treated with K₂CO₃ (0.537 g, 3.89 mmol) and epibromohydrin (0.33 ml, 0.53 g, 3.9 mmol). The reaction was allowed to stir at ambient temperature overnight. After warming to 40°C for 5 hours the reaction was partitioned between EtOAc and water. The organic phase was washed four times with water, dried over
15 MgSO₄ and evaporated at reduced pressure. The residue was purified by chromatography (1-5% MeOH in DCM) to give the title product as an oil (0.614 g, 94%). NMR (300 MHz): 2.69 (m, 1H), 2.83 (m, 1H), 3.88 (m, 1H), 4.25 (m, 1H), 6.15 (d, 1H), 6.85 (d, 2H), 7.97 (t, 1H), 7.27 (t, 2H), 7.58 (d, 2H), 7.66 (d, 2H), 7.95 (d, 1H), 8.9 (s, 1H), 9.23 (s, 1H); m/z: (ES⁺) 335 (MH⁺).

20

Example 92

2-{4-[3-(*N,N*-Dimethyl)aminopropoxy]anilino}-4-(2-fluoro-5-methylanilino)pyrimidine

4-(2-fluoro-5-methylanilino)-2-(4-hydroxyanilino)pyrimidine (Reference Example H-2, 250 mg, 0.57 mmol) was dissolved in DMSO (2 ml) and K₂CO₃ (205 mg, 1.5 mmol) was
25 added. The resulting suspension was stirred for 30 mins to give a turquoise solution. 3-(*N,N*-Dimethylamino)propyl chloride HCl (122 mg, 0.77 mmol) was added and the mixture stirred at 100°C for 3 hours. To this brown solution was added DCM (20 ml) and silica (3 g). The mixture was evaporated to dryness under high vacuum and the residue loaded onto a Mega Bond Elute column (10 g) which was eluted with DCM (2 x 25 ml), 2% NH₃ in MeOH (3 x
30 25 ml), 4% NH₃ in MeOH (3 x 25 ml), 6% NH₃ in MeOH (3 x 25 ml) and 10% NH₃ in MeOH (9 x 25 ml) to give the title product as a colourless gum (75 mg, 29%). M/z (ES⁺) 396 (MH⁺),

HPLC (Hypersil 10cm base deactivated) (60% MeCN/H₂O/ 0.2% TFA) Retention time : 4.60 min.

Reference Example H-2

5 4-(2-Fluoro-5-methylanilino)-2-(4-hydroxyanilino)pyrimidine

4-(2-Fluoro-5-methylanilino)-2-chloropyrimidine (Reference Example A-10, 1.00 g, 4.2 mmol) was dissolved in NMP (5 ml) and 4-hydroxyaniline (0.41 g, 3.7 mmol) and 1M HCl in diethyl ether (4.22 ml, 4.2 mmol) was added. The reaction mixture was heated at 100°C for 15 hours, and then allowed to cool to ambient temperature. The mixture was
10 evaporated under high vacuum to give the title product as a brown oil. The residue was purified by chromatography on a Mega Bond Elute column (10 g) eluting with DCM (4 x 25 ml), 2% NH₃ / MeOH in DCM (3 x 25 ml), 4% NH₃ / MeOH in DCM (3 x 25 ml), 6% NH₃ / MeOH in DCM (10 x 25 ml to give the title product as a white solid (0.80 g, 61%). NMR (300 MHz): 2.2 (s, 3H), 6.2 (d, 1H), 6.6 (d, 2H), 6.9 (m, 1H), 7.1 (m, 1H), 7.4 (d, 2H), 7.8 (d,
15 1H), 7.9 (d, 1H), 8.7 (s, 1H), 8.8 (s, 1H), 8.9 (s, 1H); m/z: (ES⁺) 311.0 (MH⁺).

Reference Example H-3

4-(2-Fluoro-5-methylanilino)-2-(3-hydroxyanilino)pyrimidine

The title compound was prepared by an analogous method to Reference Example H-2
20 using 3-hydroxyaniline instead of 4-hydroxyaniline. NMR (300 MHz): 2.2 (s, 3H), 6.4 (m, 2H), 6.8-7.2 (m, 5H), 7.8 (d, 1H), 8.0 (d, 1H), 9.1 (m, 3H); m/z: (ES⁺) 311.0 (MH⁺).

Reference Example A-10

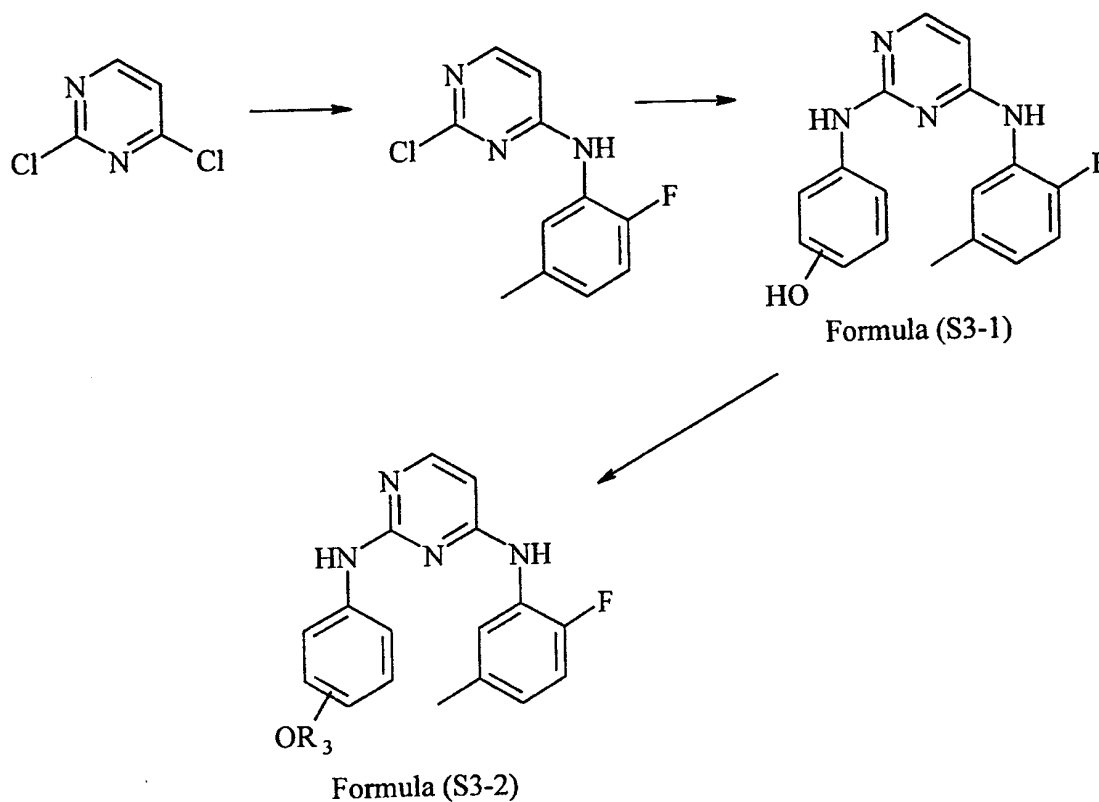
4-(2-Fluoro-5-methylanilino)-2-chloropyrimidine

25 2,4-Dichloropyrimidine (7.0 g, 47 mmol) was dissolved in *n*-butanol (5 ml), followed by addition of DIPEA (9.0 ml, 51.7 mmol), then 2-fluoro-5-methylaniline (5.3 ml, 47 mmol). The mixture was heated at 100°C overnight, and then allowed to cool to ambient temperature. The mixture was evaporated to give an oil, which was taken up in DCM (250 ml) and washed with water (3 x 50 ml), brine (50 ml), dried over MgSO₄ and evaporated to give an orange oil.
30 This was purified by column chromatography eluting with EtOAc:isohexane (10:90) to give

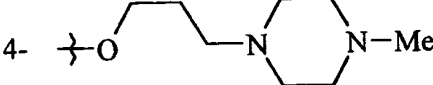
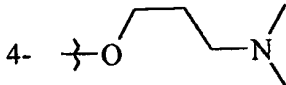
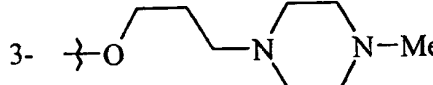
the title product as a white solid (2.40 g, 21 %). NMR (300 MHz): 2.3 (s, 3H), 6.7 (d, 1H), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (d, 1H), 8.1 (d, 1H), 9.7 (s, 1H); m/z: (ES⁺) 237.9 (MH⁺).

Examples 93-95

- 5 Examples 93-95 were prepared, according to Scheme 3, by an analogous procedure to that used for Example 92, using the appropriate 4-(2-fluoro-5-methylanilino)-2-(3- or 4-hydroxyanilino)pyrimidine of Formula (S3-1) and the appropriate commercially available haloalkylamine HCl salt.



Scheme 3

Ex No	OR ₃	m/z (MH ⁺)	HPLC (Hypersil 10cm base deactivated) Retention time 60% MeCN/H ₂ O /0.2% TFA
93	4- 	451.3	3.35 min.
94	4- 	396.2	3.85 min.
95	3- 	451.3	3.55 min.

Example 96**4-(2-Fluoro-5-methylanilino)-2-[4-(3-morpholinopropoxy)anilino]pyrimidine**

4-(2-Fluoro-5-methylanilino)-2-chloropyrimidine (Reference Example A-10, 140 mg, 0.6 mmol) was dissolved in dry NMP (2 ml) and 4-(3-morpholinopropoxy)aniline.2.HBr salt (see CAS Registry No. 100800-40-6; J.Am.Chem.Soc., 76, 1954, 4396; 188 mg, 0.5 mmol) added. The mixture was stirred at ambient temperature for 5 minutes, then checked to ensure the reaction mixture was acidic (pH 1) and heated at 100°C for 3 hours. The mixture was allowed to cool and evaporated to dryness to give an oil. Silica (2 g) and DCM (10 ml) were added and the mixture then re-evaporated to dryness and purified by chromatography on a Mega Bond Elute column (10 g) (eluting with DCM (2 x 25 ml), 2% NH₃ in MeOH (3 x 25 ml), 4% NH₃ in MeOH (3 x 25 ml), 6% NH₃ in MeOH (3 x 25 ml), 10% NH₃ in MeOH (9 x 25 ml)) to give the title product as a colourless oil, which was triturated with diethyl ether to give a white solid (95 mg, 46%). NMR (300 MHz): 1.8 (m, 2H), 2.2 (s, 3H), 2.4 (m, 4H), 2.4 (m, 2H), 3.6 (t, 3H), 3.9 (t, 2H), 6.2 (d, 1H), 6.8 (d, 2H), 6.9 (m, 1H), 7.1 (m, 1H), 7.5 (d, 2H), 7.8 (d, 1H), 8.0 (d, 1H), 8.9 (s, 2H); m/z: (ES⁺) 438.2 (MH⁺).

Example 97

2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropyl(*N*-methyl)amino]anilino}-4-(2-fluoro-5-methylanilino)pyrimidine

By a procedure analogous to Example 96, 4-(2-fluoro-5-methylanilino)-2-chloropyrimidine (Reference Example A-10) and 4-[3-(*N,N*-dimethyl)amino-2-hydroxypropyl(*N*-methyl)amino]aniline (Reference Example D-2) were reacted to give the title product as a brown oil (60 mg, 17%). M/z: (ES⁺) 425.3 (MH⁺). HPLC (Hypersil 10cm base deactivated) 60% MeCN/H₂O/ 0.2% TFA. Retention time : 2.66 min.

10 **Method J: Reaction of anilines with bromoalkylepoxides followed by opening of the epoxide with an amine.**

Reference Example J-1

4-[3-(*N,N*-dimethyl)amino-2-hydroxypropyl(*N*-methyl)amino]nitrobenzene

4-Nitro-*N*-methylaniline (1.00 g, 6.6 mmol) was dissolved in DMF (50 ml) and cooled to 0°C in an ice bath. Sodium hydride (290 mg, 7.2 mmol, 60% dispersion in mineral oil) was added portionwise over 30 mins to give an orange/brown solution. To this was added epibromohydrin (0.62 ml, 7.2 mmol) dropwise and the mixture left to stir at ambient temperature for 12 hours. The mixture was evaporated to give a yellow oily residue, to which was added dimethylamine 2.0 M in MeOH (66 ml, 0.13 mol) and left to stir at ambient temperature for 12 hours. The mixture was evaporated to give a yellow solid, then taken up in DCM (100 ml), washed with H₂O (20 ml), brine (20 ml), dried over MgSO₄ and evaporated to dryness to give the title product as an orange solid (1.44 g, 86%). NMR (300 MHz): 2.2 (s, 6H), 2.3 (t, 2H), 3.1 (s, 3H), 3.3-3.6 (m, 2H), 3.8 (br s, 1H), 4.8 (d, 1H) 6.8 (d, 2H), 8.0 (d, 2H); m/z: (ES⁺) 254.0 (MH⁺).

25

Reference Example D-2

4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropyl-(*N*-methyl)amino]aniline

4-[3-(*N,N*-Dimethyl)amino-2-hydroxypropyl-(*N*-methyl)amino]nitrobenzene (Reference Example J-1, 1.30 g, 5.1 mmol) was dissolved in EtOH (150 ml) and 10% Pd/C was added (130 mg, 10% b/w). The reaction was stirred under a hydrogen balloon for 3 hours. The reaction mixture was then filtered through a pad of celite and washed thoroughly with

more EtOH. The solution was evaporated to give a brown oil. DCM was added to solubilise then 1M HCl in diethyl ether added to form the HCl salt, as a green solid in solution. The hygroscopic salt was filtered quickly, drying in a dessicator overnight to give the title product (0.80 g, 60%). M/z: (ES⁺) 224.0 (MH⁺).

5

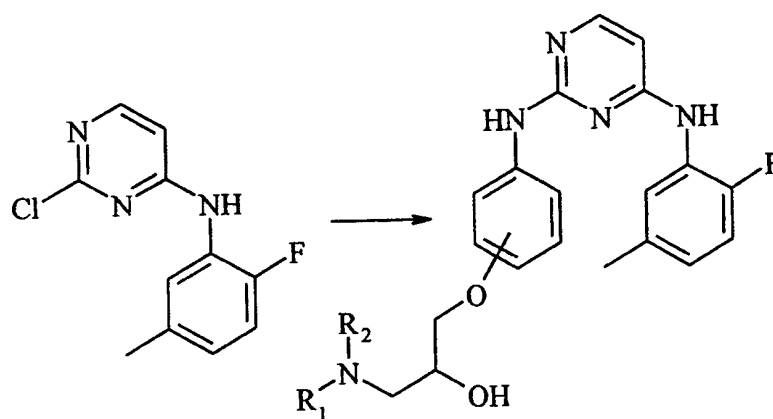
Example 98**4-(2-Fluoro-5-methylanilino)-2-[4-(3-N-isopropylamino-2-hydroxypropoxy)anilino]pyrimidine**

To a suspension of 4-(2-fluoro-5-methylanilino)-2-chloropyrimidine (Reference
10 Example A-10, 117 mg) and 4-(3-N-isopropylamino-2-hydroxypropoxy)aniline (224 mg) in *n*-butanol (1 ml) was added a 1M HCl solution in diethyl ether (0.4 ml) and the mixture warmed to remove ether, then heated at reflux for 1.5 hours. The mixture was cooled and 2M ammonia solution in methanol (2 ml) was added. The product was pre-loaded onto silica and purified by column chromatography, eluting with DCM: (2M) methanolic ammonia; 92:8, to
15 give the title product as a white solid (170 mg, 89%). NMR (300 MHz): 0.97 (6H, d), 2.26 (3H, s), 2.43-2.78 (3H, m), 3.76-3.91 (3H, m), 4.05 (1H, brs), 4.90 (1H, br s), 6.24 (1H, d), 6.77 (2H, d), 6.84-6.93 (1H, m), 7.11 (1H, dd), 7.51 (2H, d), 7.75 (1H, d), 7.96 (1H, d), 8.89 (2H, s), m/z: (ES⁺) 426 (MH⁺).

4-(3-N-Isopropylamino-2-hydroxypropoxy)aniline was prepared by analogy with
20 Reference Examples B-1, C-1 and D-1, but using isopropylamine in place of dimethylamine in Method C.

Examples 99-102

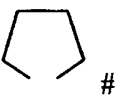
The following compounds were similarly prepared, according to Scheme 4, by an
25 analogous procedure to that used for Example 98, using the appropriate anilines (prepared by analogy with the preparation of the 4-(3-N-isopropylamino-2-hydroxypropoxy)aniline starting material of Example 98, using the appropriate amine in Method C).



Formula (S4-1)

Scheme 4

Ex No	3 or 4 *	R ₁	R ₂	NMR (300 MHz)	m/z (MH ⁺)
99	4	H	cyclo- pentyl	1.20-1.78 (8H, s), 2.26 (3H, s), 2.46-2.64 (2H, m), 2.98 (1H, m), 3.76-3.91 (3H, m), 4.86 (1H, br s), 6.24 (1H, d), 6.76 (2H, d), 6.87-6.93 (1H, m), 7.12 (1H, dd), 7.51 (2H, d), 7.74 (1H, d), 7.96 (1H, d), 8.88 (2H, s)	452
100	4	H	tert-butyl	1.01 (9H, s), 2.26 (3H, s), 2.44-2.63 (2H, m), 3.70- 3.92 (3H, m), 4.82 (1H, br s), 6.23 (1H, d), 6.76 (2H, d), 6.85-6.93 (1H, m), 7.11 (1H, dd), 7.51 (2H, d), 7.75 (1H, d), 7.96 (1H, d), 8.88 (2H, s)	440

101	4			1.59-1.74 (4H, m), 2.25 (3H, s), 2.38-2.63 (6H, m), 3.73-3.94 (3H, m), 4.76 (1H, d), 6.24 (1H, d), 6.76 (2H, d), 6.85-6.94 (1H, m), 7.11 (1H, dd), 7.50 (2H, d), 7.74 (1H, d), 7.96 (1H, d), 8.88 (2H, s)	438
102	3	H	isopropyl	0.96 (6H, d), 2.26 (3H, s), 2.41-2.75 (3H, m), 3.71-3.86 (3H, m), 4.87 (1H, d), 6.28 (1H, d), 6.45 (1H, d), 6.86-6.95 (1H, m), 6.99-7.17 (2H, m), 7.22-7.34 (2H, m), 7.75 (1H, d), 8.01 (1H, d), 8.96 (1H, s), 9.03 (1H, s)	426

* Refers to position of side chain in Formula S4-1.

So that R₁, R₂ and the nitrogen atom to which they are attached form a pyrrolidin-1-yl ring.

Example 103

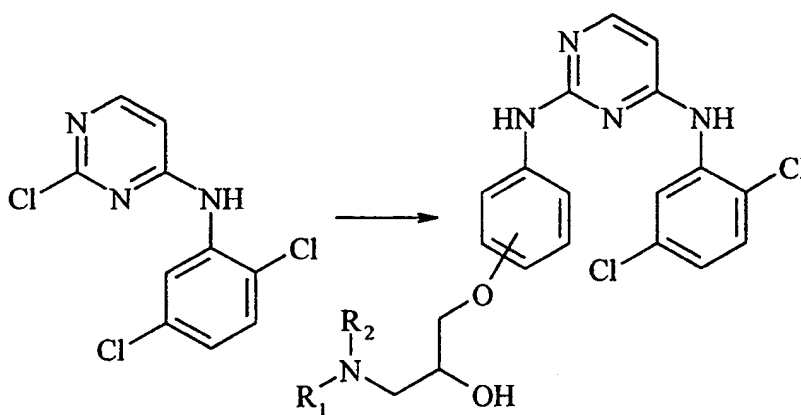
5 4-(2,5-Dichloroanilino)-2-[4-(3-*N*-isopropylamino-2-hydroxypropoxy)anilino]pyrimidine

2-Chloro-4-(2,5-dichloroanilino)pyrimidine (Reference Example A-4, 100 mg, 0.36 mmol) was dissolved in dry NMP (2 ml). 4-(2-Hydroxy-3-isopropylaminopropoxy)aniline hydrochloride (see Example 98; 90 mg, 0.35 mmol) and 1M ethereal HCl (0.8 ml) were added and the mixture heated to 100°C for 3 hours. The brown solution was partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was evaporated and the residue purified by column chromatography (7M NH₃/MeOH (4%) : DCM). The resulting solid was broken up in isohexane, filtered and dried to give the title product (100 mg, 59%). NMR (300 MHz) 0.97 (d, 6H), 2.55-2.75 (m, 3H), 3.75-3.9 (m, 3H), 6.35 (d, 1H),

6.77 (d, 2H), 7.20 (q, 1H), 7.50 (m, 3H), 8.02 (m, 2H), 8.88 (brs, 1H), 8.99 (s, 1H); m/z (ES^+) 462 (MH^+).

Examples 104-107

- 5 The following compounds were similarly prepared, according to Scheme 5, by an analogous procedure to that used for Example 103, using the appropriate anilines (prepared by analogy with the preparation of the 4-(3-*N*-isopropylamino-2-hydroxypropoxy)aniline starting material of Example 98, using the appropriate amine in Method C).

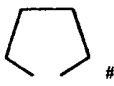


Formula (S5-1)

10

Scheme 5

Ex No	3 or 4 *	R ₁	R ₂	NMR (300 MHz)	m/z (MH^+)
104	4	H	<i>tert</i> -butyl	1.00 (s, 9H), 2.52-2.68 (m, 2H), 3.70-3.84 (m, 2H), 3.84-3.92 (m, 1H), 6.35 (d, 1H), 6.77 (d, 2H), 7.20 (q, 1H), 7.50 (m, 3H), 8.02 (m, 2H), 8.88 (brs, 1H), 8.99 (s, 1H)	476
105	3	H	isopropyl	0.97 (d, 6H), 2.5-2.73 (m, 3H), 3.80 (m, 3H), 6.38 (d, 1H), 6.45 (dd, 1H), 7.04 (t, 1H), 7.10 (m, 2H), 7.29 (dd, 1H), 7.52 (d, 1H), 7.99 (d, 1H), 8.08 (d, 1H), 8.96 (brs, 1H), 9.13 (s, 1H)	462

106	4			1.65 (m, 4H), 2.37-2.63 (m, 6H), 3.73-3.93 (m, 3H), 4.78 (brs, 1H), 6.35 (d, 1H), 6.77 (d, 2H), 7.20 (q, 1H), 7.50 (m, 3H), 8.02 (m, 2H), 8.88 (s, 1H), 8.99 (s, 1H)	474
107	4	H	cyclopentyl	1.16 (m, 2H), 1.47 (m, 2H), 1.60 (m, 2H), 1.70 (m, 2H), 2.52-2.67 (m, 2H), 2.98 (m, 1H), 3.75-3.90 (m, 3H), 6.35 (d, 1H), 6.77 (d, 2H), 7.20 (q, 1H), 7.50 (m, 3H), 8.02 (m, 2H), 8.88 (s, 1H), 8.99 (s, 1H)	488

* Refers to position of side chain in Formula S4-1.

So that R₁, R₂ and the nitrogen atom to which they are attached form a pyrrolidin-1-yl ring.

Example 108

- 5 The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

- 91 -

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

- 92 -

(g): Injection III	(1mg/ml,buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

5

10

15

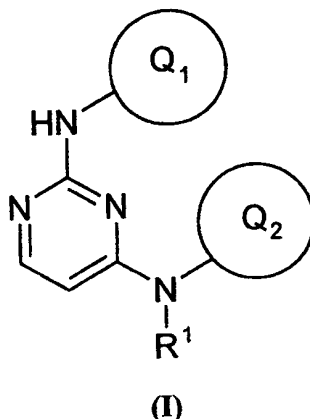
20

25

CLAIMS

What is claimed is :

1. A pyrimidine derivative of the formula (I)

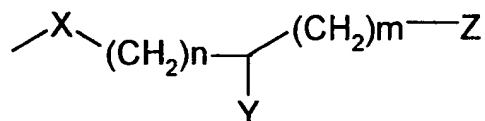


5

wherein

- R¹ is selected from hydrogen, (1-6C)alkyl [optionally substituted by one or two substituents independently selected from halo, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, hydroxy, cyano, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl, -NHCO(1-4C)alkyl, trifluoromethyl, phenylthio, phenoxy, pyridyl, morpholino], benzyl, 2-phenylethyl, (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], N-phthalimido-(1-4C)alkyl, (3-5C)alkynyl [optionally substituted by one phenyl substituent] and (3-6C)cycloalkyl-(1-6C)alkyl;
- 15 wherein any phenyl or benzyl group in R¹ is optionally substituted by up to three substituents independently selected from halogeno, hydroxy, nitro, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, cyano, trifluoromethyl, (1-3C)alkyl [optionally substituted by 1 or 2 substituents independently selected from halogeno, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, hydroxy and trifluoromethyl], (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (3-5C)alkynyl, (1-3C)alkoxy, -SH, -S-(1-3C)alkyl, carboxy, (1-3C)alkoxycarbonyl;
- 20 Q₁ and Q₂ are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-tetrahydronaphthyl;

and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of the formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia)



5

(Ia)

[provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH-link];

wherein

X is CH₂, O, S, NH or NR_x [wherein R_x is (1-4C)alkyl, optionally substituted by one

10 substituent selected from halo, amino, cyano, (1-4C)alkoxy or hydroxy];

Y is H or as defined for Z;

Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino;

15 n is 1, 2 or 3; m is 1, 2 or 3;

and Q₁ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],

20 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl,

25 N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H₂N-CO-NH-),

(1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;

5 and also independently, or in addition to, the above substituents, Q₁ may optionally bear on any available carbon atom up to two further substituents independently selected from (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

15 and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkoxy, cyano-(1-4C)alkoxy, carbamoyl-(1-4C)alkoxy, N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy, 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy, 2-di-[(1-4C)alkyl]aminoethoxy, (1-4C)alkoxycarbonyl-(1-4C)alkoxy, halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy, 2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy,

(3-5C)alkenyloxy, (3-5C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido ($H_2N-CO-NH-$), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio, phenoxy and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

2. A pyrimidine derivative of the formula (I) as claimed in claim 1, wherein R^1 is hydrogen, benzyl, (3-5C)alkynyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-4C)alkyl [optionally substituted by one or two substituents independently selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups or one phenyl substituent;
- Q_1 and Q_2 are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-tetrahydronaphthyl;
- and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula (Ia) and Q_2 may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q_1 the substituent of formula (Ia) is not adjacent to the -NH- link];
- X is CH_2 , O, S, NH or NR_x [wherein R_x is (1-4C)alkyl, optionally substituted by one substituent selected from halo, amino, cyano, (1-4C)alkoxy or hydroxy];
- Y is H or as defined for Z;

Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino; n is 1, 2 or 3; m is 1, 2 or 3;

5

and Q₁ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],

- (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H₂N-CO-NH-), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;

and also independently, or in addition to, the above substituents, Q₁ may optionally bear on any available carbon atom up to two further substituents independently selected from

- (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

- and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, 5 fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-10 (1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkoxy, cyano-(1-4C)alkoxy, carbamoyl-(1-4C)alkoxy, N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy, N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy, 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy, 2-di-[(1-4C)alkyl]aminoethoxy, (1-4C)alkoxycarbonyl-(1-4C)alkoxy, 15 halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy, 2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy, (3-5C)alkenyloxy, (3-5C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H₂N-CO-NH-), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, 20 di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents independently selected from 25 (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, 30 phenylthio, phenoxy and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a

pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

3. A pyrimidine derivative of the formula (I) as claimed in claim 1 or 2, wherein
 R^1 is hydrogen, benzyl, (3-5C)alkynyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-4C)alkyl [optionally
- 5 substituted by one or two substituents independently selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups or one phenyl substituent;
 Q_1 and Q_2 are independently selected from phenyl or indanyl;
 and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the
- 10 formula (Ia) and Q_2 may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q_1 the substituent of formula (Ia) is not adjacent to the -NH- link];
 X is CH_2 , O, S, NH or NR_x [wherein R_x is (1-4C)alkyl, optionally substituted by one substituent selected from halo, amino, cyano, (1-4C)alkoxy or hydroxy];
- 15 Y is H or as defined for Z ;
 Z is OH, SH, NH_2 , (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino;
 n is 1, 2 or 3; m is 1, 2 or 3;
- 20 and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;
- 25 and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino,
- 30 and also independently, or in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from

phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

4. A pyrimidine derivative of the formula (I) as claimed in any of claims 1 to 3, wherein
- 5 R¹ is hydrogen, benzyl, (3-5C)alkynyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-4C)alkyl [optionally substituted by one or two substituents independently selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups or one phenyl substituent;
- Q₁ and Q₂ are independently selected from phenyl or indan-5-yl;
- 10 and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of the formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link];
- X is O; Y is H or OH and Z is -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl,
- 15 pyrrolidin-1-yl or piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl]; n is 1 or 2 and m is 1 or 2;
- and Q₁ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],
- 20 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino; and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],
- 25 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents independently selected from phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or
- 30 in-vivo-hydrolysable ester thereof.

5. A pyrimidine derivative of the formula (I) as claimed in any of claims 1 to 4, wherein
R¹ is -CH₂CH=CHBr, -CH₂CH₂CH₂CF₃ or -CH₂CH=CH-phenyl;
Q₁ and Q₂ are independently selected from phenyl or indan-5-yl;
and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of the
5 formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of
the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not
adjacent to the -NH- link];
X is O; Y is H or OH and Z is -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl,
pyrrolidin-1-yl or piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or
10 (1-4C)alkanoyl]; n is 1 or 2 and m is 1 or 2;
and Q₁ may optionally bear on any available carbon atom up to four substituents
independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally
substituted by up to three halo substituents, or by one trifluoromethyl substituent],
(2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,
15 fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;
and Q₂ may optionally bear on any available carbon atom up to four substituents
independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl
[optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],
(2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,
20 fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino,
and also independently, or in addition to, the above optional substituents, Q₂ may optionally
bear on any available carbon atom up to two further substituents independently selected from
phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or
in-vivo-hydrolysable ester thereof.
25
6. A pyrimidine derivative of the formula (I) as claimed in any of claims 1 to 5, wherein
R¹ is -CH₂CH=CHBr, -CH₂CH₂CH₂CF₃ or -CH₂CH=CH-phenyl;
Q₁ and Q₂ are both phenyl;
Q₁ bears on any available carbon atom one substituent of the formula (Ia) [provided that the
30 substituent of formula (Ia) is not adjacent to the -NH- link];

X is O; Y is H or OH and Z is -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl or piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl]; n is 1 or 2 and m is 1 or 2;

and Q₁ may optionally bear on any available carbon atom up to four substituents

5 independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino; and Q₂ may optionally bear on any available carbon atom up to four substituents

10 independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q₂ may optionally
15 bear on any available carbon atom up to two further substituents independently selected from phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

7. A pyrimidine derivative of the formula (I) as described in claim 5 or 6, other than that
20 R¹ is H; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

8. A pyrimidine derivative of the formula (I) as claimed in claim 1, being:

2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-bromo-4-methylanilino)pyrimidine;

25 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloroanilino)pyrimidine;

2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(3,4-dichloroanilino)pyrimidine;

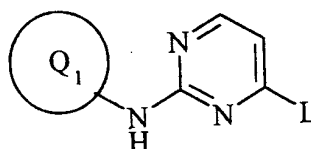
2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,4-difluoro-
30 (N-cyanomethyl)anilino)pyrimidine;

2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-

- 2-fluoroethyl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(*N*-propyn-2-yl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-
 5 (N-cyanomethyl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methylanilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-cyanoanilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-
 10 (N-2,2-difluoroethyl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-4,4,4-trifluorobutyl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-3-phenylprop-2-enyl)anilino)pyrimidine;
 15 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methyl-(N-4,4,4-trifluorobutyl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methyl-(N-3-bromoprop-2-enyl)anilino)pyrimidine;
 2-{4-[3-(*N,N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methyl-(N-3-
 20 phenylprop-2-enyl)anilino)pyrimidine;
 or pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.

9. A process for the preparation of a compound of the formula (I) as claimed in claim 1, which comprises of a) to h) :-

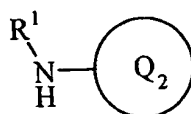
25 a) reacting a pyrimidine of formula (II):



(II)

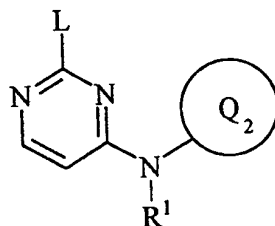
wherein L is a displaceable group as defined below, with a compound of formula (III):

- 104 -



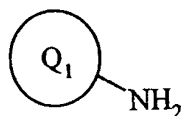
(III)

b) reaction of a pyrimidine of formula (IV):



(IV)

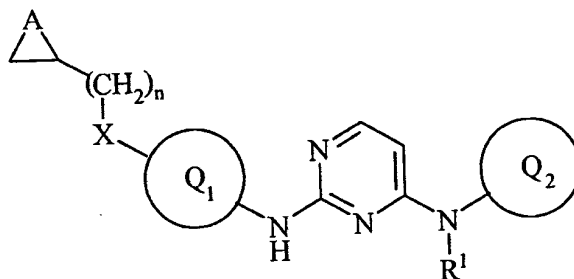
wherein L is a displaceable group as defined below, with a compound of formula (V):



(V)

10

c) for compounds of formula (I) wherein n is 1, 2 or 3; m = 1 and Y is OH, NH₂ or SH :
reaction of a 3-membered heteroalkyl ring of formula (VI):



(VI)

15 wherein A is O, S or NH;

with a nucleophile of formula (VII):

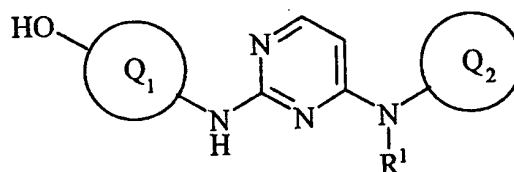
Z-D

(VII)

wherein D is H or a suitable counter-ion;

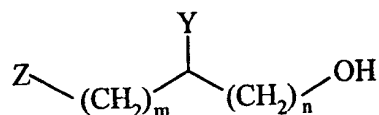
d) for compounds of formula (I) where X is oxygen :

reaction of an alcohol of formula (VIII):



(VIII)

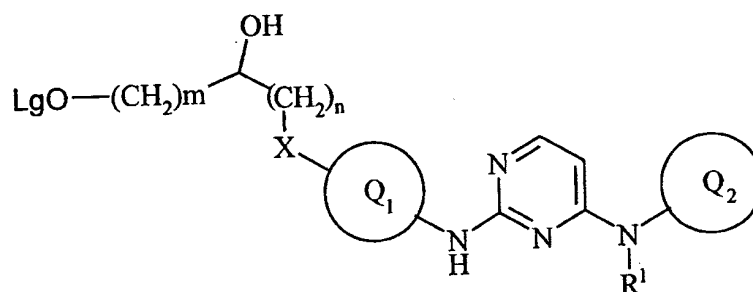
5 with an alcohol of formula (IX):



(IX)

e) for compounds of formula (I) wherein X is CH₂, O, NH or S; Y is OH and m is 2 or 3 :

10 reaction of a compound of formula (X) :



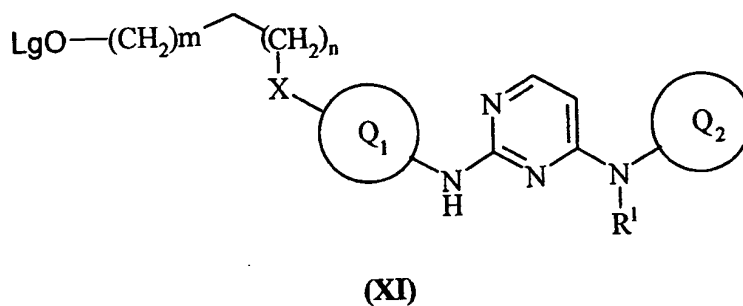
(X)

15 wherein -OLg is a leaving group such as mesylate or tosylate; with a nucleophile of formula

Z-D (VII) wherein D is H or a suitable counter-ion;

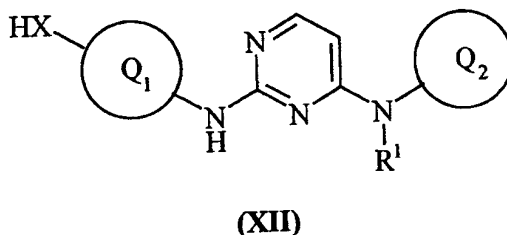
f) for compounds of formula (I) wherein X is CH₂, O, NH or S; Y is H; n is 1, 2 or 3 and m is

1, 2 or 3 : reaction of a compound of formula (XI) :

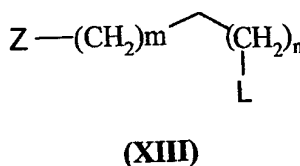


wherein -OLg is a leaving group such as mesylate or tosylate; with a nucleophile of formula

- 5 Z-D (VII) wherein D is H or a suitable counter-ion;
 g) for compounds of formula (I) wherein X is O, NH or S; Y is H; n is 1, 2 or 3 and m is 1, 2 or 3 : reaction of a compound of formula (XII) with a compound of formula (XIII) :



10



or

- 15 h) for compounds of formula (I) in which Z is SH, by conversion of a thioacetate group in a corresponding compound; and thereafter if necessary:
 i) converting a compound of the formula (I) into another compound of the formula (I);
 ii) removing any protecting groups;
 iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester; wherein L is a
 20 displaceable group and D is hydrogen or a counter-ion.

10. A method for producing an anti-cancer effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the formula (I)

as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

11. A compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-
5 acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament.
12. The use of a compound of the formula (I) as claimed in claims 1 to 8, or a
pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of
a medicament for use in the production of an anti-cancer effect in a warm blooded animal.
- 10 13. A pharmaceutical composition which comprises a compound of the formula (I) as
claimed in claims 1 to 8, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable
ester thereof, and a pharmaceutically-acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

In national Application No

PCT/GB 99/02790

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/48 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 19065 A (CELLTECH THERAPEUTICS) 29 May 1997 (1997-05-29) page 1 -page 22; claims 1,9,10; examples 51-54,95	1,8,9, 11,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

24 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/02790

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/GB 99/02790

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719065 A	29-05-1997	AU 7631496 A	11-06-1997
		EP 0862560 A	09-09-1998
		US 5958935 A	28-09-1999